HANDOUT 1

Day 2 - Unblinding Case

Study Protocol – CB123-201

An Expanded Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial to Assess the Safety, Tolerability, and Pharmacokinetics of Drug X When Administered Orally for 14 Days in Healthy Subjects

Trial Type: Phase 3 expanded safety trial with pharmacokinetics
Population: At least 422 randomized healthy male and female volunteers aged 18 to 80 years
Number of Sites: Approximately 12
Study Duration: Approximately 12 months
Subject Participation Duration: 6 weeks
Screening Period: 2 weeks
Treatment Period: 2 weeks
Post-Treatment Period: 2 weeks
Enrollment Lead-in Cohort: 40 subjects will be randomized at a 4:1 Drug X:Placebo ratio (Drug X, n = 32; Placebo, n = 8)
Expanded Study: Approximately 382 additional subjects will be randomized at a 4:1 ratio (Drug X, n = 306; Placebo n = 76)

STUDY TREATMENTS:
Investigational Drug: Oral Drug X capsules twice daily in fed or fasted state for 14 days
Comparator/Control: Matching placebo capsules twice daily in fed or fasted state for 14 days

OBJECTIVES:
Primary Objective
The primary objective is to determine the safety and tolerability of oral Drug X twice daily for 14 days in adult subjects.

Secondary Objective
The secondary objective is to determine the pharmacokinetics of Drug X in the Lead-in cohort (n=40 subjects).

STUDY DESIGN:
This is a multicenter, double-blind, randomized, placebo-controlled, phase 3 study to assess the safety, tolerability, and PK of oral Drug X twice daily for 14 days in adult subjects. The study is designed with a Lead-in cohort of 40 subjects to evaluate the PK of oral Drug X twice daily for 14 days in 20 fed and 20 fasted subjects. Pharmacokinetic and safety data will be reviewed after the Lead-In cohort has been completed.

After the Lead-in cohort data are reviewed, approximately 382 additional subjects will be enrolled into the expanded portion of the study. These subjects will receive study drug within 30 minutes of eating. The randomization ratio of Drug X to placebo is 4:1 for both the Lead-in cohort and the expanded study.

PK Collection
Blood will be collected at specific time points to determine the PK of Drug X. Blood samples from approximately 40 subjects will be evaluated for PK analysis at the targeted dose level identified by the Lead-in cohort of the study. Pharmacokinetic collection and data analysis will be evaluated from 20 subjects in the Lead-in cohort in a fasted state and 20 subjects in a fed state.

PRIMARY ENDPOINT: SAFETY
The primary outcome measure is the evaluation of the safety and tolerability of twice daily oral dosing of Drug X for 14 days through assessments and procedures such as vital sign measurements, complete and symptom-directed PEs, hematology and blood chemistry laboratory tests, pregnancy testing, ECGs, collection of AEs, and review of concomitant medications.

SECONDARY ENDPOINT: PHARMACOKINETICS
The secondary outcome measures will assess the PK of oral Drug X twice daily in subjects through collection of PK samples at specified time points. Common PK parameters will be evaluated after the initial dose (Day 1) and after multiple dosing (Day 14).

RANDOMIZATION PROCEDURES
The study is planned to enroll at least 422 subjects in the Lead-in cohort and expanded study. The Lead-in cohort of 40 subjects will be enrolled at up to 2 sites with 32 subjects receiving active study drug (16 fed and 16 fasted) and 8 subjects receiving placebo (4 fed and 4 fasted).

All subjects in the expanded study (n = 382) will take study medication in a fed state before dosing. Subjects will be enrolled at approximately 12 sites and randomly assigned to treatment with 306 subjects receiving Drug X and 76 subjects receiving placebo.

An Interactive Web Response System (IWRS) will be utilized to randomly assign treatment for the 40 subjects who will participate in the PK portion of the study at 2 selected Lead-In cohort sites. For the expanded study, it is expected that approximately 450 male and female subjects will be screened in order to enroll a total of 382 subjects. Of the 382 subjects, 306 subjects will be randomly assigned to receive Drug X and 76 subjects to receive placebo. The IWRS will facilitate the random assignment of treatment for subjects in the trial.

Subjects will be assigned to treatment groups in a 4:1 ratio (Drug X: placebo) based on a computer-generated central randomization schedule prepared before enrollment into the

Lead-in cohort and expanded portion of the study. The randomization will be balanced by using permuted blocks of an appropriate size.

Randomization will occur on Day 1 after informed consent has been obtained and it has been confirmed that the subject fulfills all eligibility criteria. The investigator or delegated site personnel will access the IWRS and enter the site number, subject number, and subject's date of birth.

The IWRS will assign a randomization number that is used to link the subject to 1 of the 2 treatment arms (4:1 ratio). The IWRS also specifies the study drug bottle numbers to be assigned to the subject (the study drug bottle numbers match the treatment arm assigned by the randomization list). The assigned study drug bottles will be dispensed to the subject by the site. The randomization code will not be broken or made available to study subjects or their families, investigators, clinical personnel, or site managers until all subjects have completed the double-blind phase of the trial and the database has been closed in accordance with standard operating procedures (SOPs).

BLINDING

This study will be performed as a double-blind study. All parties involved with the study will remain blinded to the treatment until study completion. Under routine circumstances, the blind will not be broken. Requests for unblinding of a subject's randomization assignment will be made through the IWRS after consultation with the medical monitor who will provide the IWRS access code appropriate for that subject. Subject code breaks by the investigator will result in withdrawal of the subject from the trial. The date, time, and reason for the unblinding must be documented in the appropriate page of the electronic case report form (eCRF), and the sponsor must be informed as soon as possible.

Medicines & Healthcare products Regulatory Agency

U.S. FOOD & DRUG ADMINISTRATION

Unblinding Case Study

Charles Bonapace, CDER/FDA
Jean Mulinde, CDER/FDA
Gail Francis, MHRA

Unblinding Case Study

- 5 min Introduction/Background
- 30 min Group Discussion
- 15 min Group Report-out
- 10 min Case Wrap-up

Background - Study CB123-201

- Multicenter, double-blind, placebo-controlled, randomized study to assess the safety, tolerability, and PK of oral Drug X twice daily for 14 days in healthy adult subjects
- Lead-in cohort (n=40) at sites 101 and 102 to evaluate the PK of oral Drug X twice daily for 14 days in fed and fasted subjects

Background - Study CB123-201

- After the Lead-in cohort data are reviewed by the sponsor, 382 additional subjects will be enrolled into the expanded portion of the study at 10 additional sites
- Randomization ratio of Drug X to placebo is 4:1 for the Lead-in cohort and expanded portion

Assignment

- You are an auditor examining the records of an investigator at site 101 (one of the Lead-in sites)
- While auditing the records, you identify the attached collection of documents to further discuss with site staff

Assignment

- Study protocol – CB123-201
- Emails
- Subset of an IWRS data
- Label from dispensed kit 1236
- Shipping order for site 101
- Certificate of Analysis for Drug X and placebo
- Treatment Emergent AEs
- Pharmacokinetic parameters

Group Discussion

- 30 min for group discussion/case questions
- Facilitators are available to clarify any questions

Wrap-Up (1)

What concerns do you have related to the documents you identified at your site?

- Emails sent from sponsor accidently included site 101
- IWRS table linking subject number and lot number
- Shipping order identifies the lot number and kit number of 16 Drug X kits (all 16 kits dispensed kits at site 101)
- Shipping order identifies the lot number and kit number of 8 placebo kits (3/8 dispensed kits at site 101)

Wrap-Up (2)

- CoAs containing the lot number for Drug X and placebo
- CoA of placebo containing 24 kits numbers (8/8 dispensed placebo kits at sites 101 and 102)
- Treatment-Emergent AE table demonstrating Metallic Taste was associated with Drug X (10/32 [31.3%] vs. 1/8 [12.5%])
- Pharmacokinetic data table providing Cmax values from 40 subjects who competed the Lead-in phase (sites 101 and 102)

Wrap-Up (3)

Were any study subjects at this site unblinded?

Lot Number	Description	No. of Cartons	Packed By
5-MIC-158-1	Kit Nos. 1234, 1345, 1456, 2360, 3246, 3456, 3397, 4456	1	CB
82356-64-01	Kit Nos. 48, 471, 1025, 1171, 1236, 1257, 1425, 1981, 2301, 2851, 3357, 3361, 3412, 3454, 4062, 4894	2	CB

Three placebo kits and all 16 Drug X kits were unblinded in the shipping order

Wrap-Up (4)

Were any study subjects at this site unblinded?

STUDYID	USUBJID	SUBJID	SITEID	TRTPN	PART	FASTSTAT	IDUNIQUE	PARAM	PARAMCD	PARAMN	PARAMFL	PARAMCMAX	ANL01FL
CB123-201	CB123-201-101-101	101-101	101	2	Lead-in Cohort	FED	3412	Max Conc ng/mL	CMAX	37	Y	2641	Y
CB123-201	CB123-201-101-102	101-102	101	2	Lead-in Cohort	FED	4062	Max Conc ng/mL	CMAX	37	Y	1490	Y
CB123-201	CB123-201-101-103	101-103	101	2	Lead-in Cohort	FED	1981	Max Conc ng/mL	CMAX	37	Y	1910	Y
CB123-201	CB123-201-101-104	101-104	101	2	Lead-in Cohort	FED	1234	Max Conc ng/mL	CMAX	37	Y	BLQ	Y

The treatment assignment of all 20 subjects at site 101 was identified based on Cmax values in the PK parameters

Wrap-Up (5)

Were any study subjects at this site unblinded?

Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	SubjectNumber	NULL	102-114	2015-02-25 15:31:11.839	Brent, David	230512	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	DisplayNumber	NULL	88203851	2015-02-25 15:31:11.839	Brent, David	230513	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	Unblinded	NULL	0	2015-02-25 15:31:11.839	Brent, David	230514	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	Treatment	NULL	1	2015-02-25 15:31:11.839	Brent, David	230515	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	LotId	NULL	82356-64-101	2015-02-25 15:31:11.839	Brent, David	230516	42810

The lot number of the treatment assignment of all subjects in study CB123-201 was identified in the IWRS data

Wrap-Up (6)

Were any study subjects at this site unblinded?

	Placebo (N=8)			Drug X (N=32)			Total (N=40)		
SYSTEM ORGAN CLASS									
Preferred Term Grade	**Grade**	**n**	**% (n/N)**	**Grade**	**n**	**% (n/N)**	**Grade**	**n**	**% (n/N)**
Gastrointestinal Disorders									
Metallic taste	**Total**	1	12.5	**Total**	10	31.3	**Total**	11	27.5
	1	1	12.5	1	4	12.5	1	5	12.5
	2	0	0.0	2	2	6.3	2	2	5.0
	3	0	0.0	3	3	9.4	3	3	7.5
	4	0	0.0	4	1	3.1	4	1	2.5
	5	0	0.0	5	0	0.0	5	0	0.0
	>=3	0	0.0	>=3	5	15.6	>=3	5	12.5

Staff and study subjects may assume they are aware of the treatment assignment

Wrap-Up (7)

What is the likelihood that you are aware of the treatment allocation at other sites?

- IWRS data provides the lot number of the treatment assignment of all subjects in study CB123-201
- CoA for placebo may contains kit numbers at other sites

Wrap-Up (8)

Assuming the study progresses and enrollment is ongoing at the remaining 10 sites, do you have any concerns that unblinding may be an issue at those sites?

- Shipping records may contain lot numbers and kit numbers
- Investigators at other sites may have accidently received information via email
- CoAs link the treatment identify with lot numbers
- Treatment-Emergent AEs

Wrap-Up (9)

Can you remedy any data integrity concerns related to the conduct of this study? If so, how?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

HANDOUT 2

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Study Protocol – CB123-201

The primary objective of Study CB123-201 is to determine the safety and tolerability of oral Drug X twice daily for 14 days in adult subjects. The secondary objective is to determine the pharmacokinetics of Drug X in the Lead-in cohort (n=40 subjects).

Sites 101 and 102 participated in the Lead-In cohort and each site enrolled 20 of the 40 healthy male and female subjects. All subjects at each of these two sites had blood samples collected for PK assessment to maintain the blind (Drug X and placebo). The enrollment at these two sites participating in the Lead-In cohort is now complete.

The sponsor in in the process of reviewing the pharmacokinetic and safety data from the Lead-In cohort. After the pharmacokinetic and safety data are reviewed, subject enrollment in the expanded portion of the study (10 additional sites) will begin.

You are an auditor examining the records of an investigator participating in Study CB123-201 at site 101, one of two of the Lead-In cohort sites where the study is being conducted. The leftover bottles from the study medication (Drug X or placebo) remain at the site. The site's files are somewhat disarrayed, but you identify the attached collection of documents to further discuss with site staff.

Questions

1. What concerns do you have related to the documents you identified at your site?
2. Were any study subjects at this site unblinded?
    a. If yes, how were they unblinded?
    b. How many subjects were potentially unblinded?
    c. Who potentially knows the treatment allocation of these subjects?
3. What is the likelihood that you are aware of the treatment allocation at other sites?
4. Assuming the study progresses and enrollment is opened at the remaining 10 sites, do you have any concerns that unblinding may be an issue at those sites? If so, what are your concerns and how would you prevent a recurrence of issues identified at site 101?
5. Can you remedy any data integrity concerns related to the conduct of this study? If so, how?

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BLINDING

This study will be performed as a double-blind study. All parties involved with the study will remain blinded to the treatment until study completion. Under routine circumstances, the blind will not be broken. Requests for unblinding of a subject's randomization assignment will be made through the IWRS after consultation with

the medical monitor who will provide the IWRS access code appropriate for that subject. Subject code breaks by the investigator will result in withdrawal of the subject from the trial. The date, time, and reason for the unblinding must be documented in the appropriate page of the electronic case report form (eCRF), and the sponsor must be informed as soon as possible.

Kinetics, Thomas

From: IRTrUS <ddawn@IRTrUS>
Sent: May 1, 2015
To: CB CB@CBPharmaceuticals.com
CC: TKinetics tkinetics@greatkineticsclinicaltrials.com

Morning Chuck,
Please see attached for IRT Report requested.
Best,
Deborah

Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	GeneratedLocalDate	NULL	2015-03-08 00:00:00.000	2015-02-25 15:31:11.807	Brent, David	230494	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	IsNotificationSent	NULL	0	2015-02-25 15:31:11.807	Brent, David	230495	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	SiteId	NULL	102	2015-02-25 15:31:11.807	Brent, David	230496	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	SubjectID	NULL	7C747D16-1858-11E6-	2015-02-25 15:31:11.807	Brent, David	230497	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	SubjectVisitId	NULL	172F7D4S8-89-Y7G5W2C4	2015-02-25 15:31:11.807	Brent, David	230498	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	ResendAttempts	NULL	0	2015-02-25 15:31:11.807	Brent, David	230499	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	Status	NULL	64	2015-02-25 15:31:11.807	Brent, David	230500	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	NextVisitId	CMP	NULL	2015-02-25 15:31:11.807	Brent, David	230501	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	NextVisitName	NULL	Day 14(study completion)	2015-02-25 15:31:11.807	Brent, David	230502	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	LastVisitId	NULL	RAND	2015-02-25 15:31:11.807	Brent, David	230503	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	NextVisitDate	NULL	2015-03-22 00:00:00.000	2015-02-25 15:31:11.807	Brent, David	230504	42810
Notifications	[Id]=N'780756E5-3C75-11E6-80D1-005056967251	INSERT	CompletionDate	NULL	2015-03-22 00:00:00.000	2015-02-25 15:31:11.807	Brent, David	230505	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	Initials	NULL	DEP	2015-02-25 15:31:11.839	Brent, David	230506	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	DateOfBirth	NULL	1960-03-28 00:00:00.000	2015-02-25 15:31:11.839	Brent, David	230507	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	Gender	NULL	1	2015-02-25 15:31:11.839	Brent, David	230508	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	Status	NULL	2	2015-02-25 15:31:11.839	Brent, David	230509	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	ScreeningNumber	NULL	00123	2015-02-25 15:31:11.839	Brent, David	230510	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	ScreeningDate	NULL	2015-03-04 00:00:00.000	2015-02-25 15:31:11.839	Brent, David	230511	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	SubjectNumber	NULL	102-114	2015-02-25 15:31:11.839	Brent, David	230512	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	DisplayNumber	NULL	88203851	2015-02-25 15:31:11.839	Brent, David	230513	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	Unblinded	NULL	0	2015-02-25 15:31:11.839	Brent, David	230514	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	Treatment	NULL	1	2015-02-25 15:31:11.839	Brent, David	230515	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	LotId	NULL	82356-64-101	2015-02-25 15:31:11.839	Brent, David	230516	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	NextVisitID	NULL	RAND	2015-02-25 15:31:11.839	Brent, David	230517	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	nextVisitDate	NULL	2015-03-20 00:00:00.000	2015-02-25 15:31:11.839	Brent, David	230518	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	SiteID	NULL	102	2015-02-25 15:31:11.839	Brent, David	230519	42810

Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	InformedConsentDate	NULL	2015-03-04 00:00:00.000	2015-02-25 15:31:11.839	Brent, David	230520	42810
Subjects	[SubjectId]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	Id	NULL	8C63-33A3BF22C615	2015-02-25 15:31:11.839	Brent, David	230521	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	SubjectId	NULL	7C747D16-1858-11E6-	2015-02-25 15:31:11.852	Brent, David	230522	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	SubjectStatus	NULL	64	2015-02-25 15:31:11.852	Brent, David	230523	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	VisitIndex	NULL	1716	2015-02-25 15:31:11.852	Brent, David	230524	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	VisitId	NULL	SCR	2015-02-25 15:31:11.852	Brent, David	230525	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	TransactionLocalDateTime	NULL	2015-02-25 09:43:11.413	2015-02-25 15:31:11.852	Brent, David	230526	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	TransactionUtcDateTime	NULL	2015-02-25 14:43:11.413	2015-02-25 15:31:11.852	Brent, David	230527	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	VisitDate	NULL	2015-02-25 00:00:00.000	2015-02-25 15:31:11.852	Brent, David	230528	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	lsReplacementVisit	NULL	0	2015-02-25 15:31:11.852	Brent, David	230529	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	lsOutOfWindowVisit	NULL	0	2015-02-25 15:31:11.852	Brent, David	230530	42810
SubjectVisits	[Id]=N'780756E5-3C75-11E6-80D1-005056967251'	INSERT	SubjectVisitID	NULL	780756E5-3C75-11E6-80D1	2015-02-25 15:31:11.852	Brent, David	230531	42810

NOTE: The table above represents a subset of the entire 998 page report that was emailed to the investigator.

Label affixed to dispensed drug bottle

Kit No.: 1236

Protocol No.: CB123-201

Contents: Twenty-eight (28) capsules of Placebo or Drug X.

Instructions: One capsule by mouth twice daily in fed or fasted state for 14 days.

Store at room temperature between 15°C and 30°C. Do not Freeze

For Clinical trial use only.

Subject no.: 105

Investigator name: 

Site No.: 101

Sponsor: CB Pharmaceuticals, Inc., 10000 New Worcestershire Ave, Silver Spring, MD 20993

Tel: 1-555-255-5356

CB PHARMACEUTICALS, INC. SHIPPING ORDER

To: Thomas Kinetics
Great Kinetics Clinical Trials
101 Pharmacokinetic Drive
Lutherville, MD 21230

From: CB Pharmaceutical, INC.
10000 New Worcestershire Ave
Silver Spring, MD 20993

Order Number: 6456

Order Date: 02/23/2015

Lot Number	Description	No. of Cartons	Packed By
5-MIC-158-1	Kit Nos. 1234, 1345, 1456, 2360, 3246, 3456, 3397, 4456	1	CB
82356-64-01	Kit Nos. 48, 471, 1025, 1171, 1236, 1257, 1425, 1981, 2301, 2851, 3357, 3361, 3412, 3454, 4062, 4894	2	CB

Store at room temperature between 15°C and 30°C. Do not Freeze

For Clinical trial use only.

Call 1-555-255-5356 to report damaged contents.

CERTIFICATE OF ANALYSIS

2 Toro Road, Toronto, ON. M3J 2J8 Canada Tel: (416) 665-9696 Fax: (416) 665-4439 E-mail: orders@trc-canada.com Website: www.trc-canada.com

1. Identification

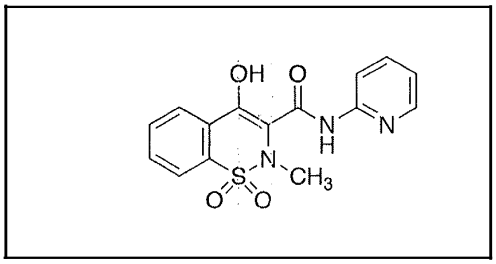
CAS Number:
36322-90-6

Catalogue Number:
P510000

Product: Drug X

Synonyms:
4-Hydroxy-2-methyl-N-2- yriinyl-2H-1,2-benzothiazine-3-carboxamide 1,1-Dioxide;
Artroxicam; Baxo; Bruxic1 ;CHF 1251; CP 16171; Caliment; Roxicam; Roxiden; Sasulen; Solocalm;

Structure:



Molecular Formula:
C1sH1aNa04S

Molecular Weight:
331.35

Source of Product:

2. Analytical Information

Lot Number:
82356-64-101

Melting Point:
196-198°C

Bolling Point:
N/A

Atmosphere:
Air

Appearance of Product:
Pale Yellow Solid

Solublllty
Chloroform, Ethyl Acetate

Method for Determlnlng'Identlty:
^{1}H NMR Spectroscopic arid Mass Spectrometric Analysis

Purity:
97%

Stability
Not determined

Long Term Storage Condition:
-20°c Freezer

Additional Information:
TLC Condition: Si02: DichJoromethane : methanol = 9 : 1; Visualized with UV and AMCS; Rf=0.55.
'H NMR and Mass spectra conform to structure.

Purchase Order Number: RO39067

QualityAssurance

QC Test Date
January 25, 2011

Retest Date
January 24, 2016

CERTIFICATE OF ANALYSIS

2 Toro Road, Toronto, ON. M3J 2J8 Canada Tel: (416) 665-9696 Fax: (416) 665-4439 E-mail: orders@nex-canada.com Website: www.nex-canada.com

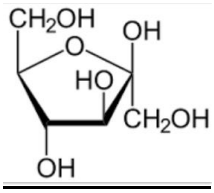
1. Identification

CAS Number: 36322-90-6 **Catalogue Number: P510000**

Product: Placebo

Synonyms:
Cellulose microcrystalline, Cellulose powder, Fructose powder, Cellulose, Cellulosum, microcrystallinum, Sugar tablets

Structure:



Molecular Formula:
C6H12O6

Molecular Weight:
180.16

Source of Product:

2. Analytical Information

Lot Number:
5-MIC-158-1

Melting Point:
196-198°C

Boiling Point:
N/A

Atmosphere:
Air

Appearance of Product:

Pale Yellow Solid

Solubility
Chloroform, Ethyl Acetate

Method for Determining Identity:
^{1}H NMR Spectroscopic and Mass Spectrometric Analysis

Purity:
97%

Stability
Not determined

Long Term Storage Condition:
-20°c Freezer

Additional Information:
TLC Condition: Si02: Dichloromethane methanol = 9: 1; Visualized with UV and AMCS; Rf=0.55. 'H NMR and Mass spectra conform to structure.

Purchase Order Number: RO39067

KIT Numbers: 1234, 1345, 1456, 1567, 1678,1789, 1890, 1280, 1290, 2345, 2346, 2347, 2348, 2349, 2350, 2360, 3245, 3246, 3348, 3456, 3568, 9967, 4456, 3397

QualityAssurance

QC Test Date
January 25, 2011

Retest Date
January 24, 2016

Kinetics, Thomas

From: PVprocessing pvprocessing@pv.com
Sent: Monday, June 1, 2015
To: CB CB@CBPharmaceuticals.com
CC: TKinetics tkinetics@greatkineticsclinicaltrials.com

Morning Chuck,
Please see attached for Treatment-Emergent AEs with max grade >=3 that you requested.
Best,
Donna

Treatment-Emergent Adverse Events with Maximum Intensity of Grade 3 or Higher by System Organ Class, Preferred Term and Maximum Intensity

CB Pharmaceuticals, INC.

Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Intensity
PK Population Safety Assessment

		Placebo (N=8)			Drug X (N=32)			Total (N=40)	
SYSTEM ORGAN CLASS									
Preferred Term	**Grade**	**n**	**% (n/N)**	**Grade**	**n**	**% (n/N)**	**Grade**	**n**	**% (n/N)**
Nervous system disorders									
Headache	**Total**	1	12.5	**Total**	3	9.4	**Total**	4	10.0
	1	0	0	1	1	3.1	1	1	2.5
	2	0	0	2	1	3.1	2	1	2.5
	3	1	12.5	3	1	3.1	3	2	5.0
	4	0	0	4	0	0	4	0	0
	5	0	0	5	0	0	5	0	0
	>=3	1	12.5	>=3	1	9.4	>=3	2	5.0
Gastrointestinal Disorders									
Metallic taste	**Total**	1	12.5	**Total**	10	31.3	**Total**	11	27.5
	1	1	12.5	1	4	12.5	1	5	12.5
	2	0	0.0	2	2	6.3	2	2	5.0
	3	0	0.0	3	3	9.4	3	3	7.5
	4	0	0.0	4	1	3.1	4	1	2.5
	5	0	0.0	5	0	0.0	5	0	0.0
	>=3	0	0.0	>=3	5	15.6	>=3	5	12.5
Abdominal pain, upper quadrant	**Total**	2	25.0	**Total**	8	25.0	**Total**	10	22.5
	1	1	12.5	1	3	9.4	1	4	10.0
	2	1	12.5	2	2	6.3	2	3	7.5
	3	0	0.0	3	2	6.3	3	2	5.0

	4	0	0.0	4	1	3.1	4	1	2.5
	5	0	0.0	5	0	0.0	5	0	0.0
	>=3	0	0.0	>=3	3	9.4	>=3	3	7.5
Musculoskeletal and Connective Tissue Disorders									
Osteoarthritis	**Total**	1	12.5	**Total**	1	3.1	**Total**	2	5.0
	1	0	0	1	1	3.1	1	1	2.5
	2	0	0.0	2	0	0	2	0	0
	3	0	0.0	3	0	0	3	0	0
	4	1	12.5	4	0	0	4	1	2.5
	5	0	0.0	5	0	0	5	0	0
	>=3	1	12.5	>=3	1	3.1	>=3	1	2.5
Respiratory, Thoracic and Mediastinal Disorders									
Pulmonary Embolism	**Total**	0	0	**Total**	1	3.1	**Total**	1	2.5
	1	0	0	1	0	0	1	0	0
	2	0	0.0	2	0	0	2	0	0
	3	0	0.0	3	0	0	3	0	0
	4	0	0.0	4	0	0	4	0	0
	5	0	0.0	5	1	3.1	5	0	0
	>=3	0	0.0	>=3	1	3.1	>=3	1	2.5

Note: N = number of subjects, n = number of subjects with event

Listing source: 16.2.7.

Program Name: xet.567020301.sas Execution Date: 31May2015

Pharmacokinetic Parameters

CB Pharmaceuticals, INC.
Page 1 of
12
Plasma Concentrations determined via LC-MS/MS, ETKO CORP., Halo UT

STUDYID	USUBJID	SUBJID	SITEID	TRTPN	PART	FASTSTAT	IDUNIQUE	PARAM	PARAMCD	PARAMN	PARAMFL	PARAMCMAX	ANL01FL
CB123-201	CB123-201-101-101	101-101	101	2	Lead-in Cohort	FED	3412	Max Conc ng/mL	CMAX	37	Y	2641	Y
CB123-201	CB123-201-101-102	101-102	101	2	Lead-in Cohort	FED	4062	Max Conc ng/mL	CMAX	37	Y	1490	Y
CB123-201	CB123-201-101-103	101-103	101	2	Lead-in Cohort	FED	1981	Max Conc ng/mL	CMAX	37	Y	1910	Y
CB123-201	CB123-201-101-104	101-104	101	2	Lead-in Cohort	FED	1234	Max Conc ng/mL	CMAX	37	Y	BLQ	Y
CB123-201	CB123-201-101-105	101-105	101	2	Lead-in Cohort	FED	1236	Max Conc ng/mL	CMAX	37	Y	4460	Y
CB123-201	CB123-201-101-106	101-106	101	2	Lead-in Cohort	FASTED	48	Max Conc ng/mL	CMAX	37	Y	1620	Y
CB123-201	CB123-201-101-107	101-107	101	2	Lead-in Cohort	FASTED	3454	Max Conc ng/mL	CMAX	37	Y	2040	Y
CB123-201	CB123-201-101-108	101-108	101	2	Lead-in Cohort	FASTED	4894	Max Conc ng/mL	CMAX	37	Y	1470	Y
CB123-201	CB123-201-101-109	101-109	101	2	Lead-in Cohort	FASTED	1425	Max Conc ng/mL	CMAX	37	Y	1440	Y
CB123-201	CB123-201-101-110	101-110	101	2	Lead-in Cohort	FASTED	1257	Max Conc ng/mL	CMAX	37	Y	1330	Y
CB123-201	CB123-201-101-111	101-111	101	2	Lead-in Cohort	FASTED	1345	Max Conc ng/mL	CMAX	37	Y	BLQ	Y
CB123-201	CB123-201-101-112	101-112	101	2	Lead-in Cohort	FASTED	2301	Max Conc ng/mL	CMAX	37	Y	2480	Y
CB123-201	CB123-201-101-113	101-113	101	2	Lead-in Cohort	FASTED	471	Max Conc ng/mL	CMAX	37	Y	3770	Y
CB123-201	CB123-201-101-114	101-114	101	2	Lead-in Cohort	FED	2851	Max Conc ng/mL	CMAX	37	Y	2510	Y
CB123-201	CB123-201-101-115	101-115	101	2	Lead-in Cohort	FED	3361	Max Conc ng/mL	CMAX	37	Y	4350	Y
CB123-201	CB123-201-101-115	101-116	101	2	Lead-in Cohort	FED	1025	Max Conc ng/mL	CMAX	37	Y	1510	Y
CB123-201	CB123-201-101-117	101-117	101	2	Lead-in Cohort	FED	3357	Max Conc ng/mL	CMAX	37	Y	1750	Y
CB123-201	CB123-201-101-118	101-118	101	2	Lead-in Cohort	FED	1456	Max Conc ng/mL	CMAX	37	Y	BLQ	Y
CB123-201	CB123-201-101-119	101-119	101	2	Lead-in Cohort	FASTED	1171	Max Conc ng/mL	CMAX	37	Y	1579	Y
CB123-201	CB123-201-101-120	101-120	101	2	Lead-in Cohort	FASTED	1567	Max Conc ng/mL	CMAX	37	Y	BLQ	Y

CB123-201	CB123-201-102-101	102-101	102	2	Lead-in Cohort	FASTED	190	Max Conc ng/mL	CMAX	37	Y	766	Y
CB123-201	CB123-201-102-102	102-102	102	2	Lead-in Cohort	FED	50	Max Conc ng/mL	CMAX	37	Y	956	Y
CB123-201	CB123-201-102-103	102-103	102	2	Lead-in Cohort	FED	1678	Max Conc ng/mL	CMAX	37	Y	BLQ	Y
CB123-201	CB123-201-102-104	102-104	102	2	Lead-in Cohort	FED	2369	Max Conc ng/mL	CMAX	37	Y	1480	Y
CB123-201	CB123-201-102-105	102-105	102	2	Lead-in Cohort	FED	3171	Max Conc ng/mL	CMAX	37	Y	2550	Y
CB123-201	CB123-201-102-106	102-106	102	2	Lead-in Cohort	FASTED	2915	Max Conc ng/mL	CMAX	37	Y	581	Y
CB123-201	CB123-201-102-107	102-107	102	2	Lead-in Cohort	FASTED	4391	Max Conc ng/mL	CMAX	37	Y	1080	Y
CB123-201	CB123-201-102-108	102-108	102	2	Lead-in Cohort	FASTED	1789	Max Conc ng/mL	CMAX	37	Y	BLQ	Y
CB123-201	CB123-201-102-109	102-109	102	2	Lead-in Cohort	FASTED	1421	Max Conc ng/mL	CMAX	37	Y	890	Y
CB123-201	CB123-201-102-110	102-110	102	2	Lead-in Cohort	FED	3626	Max Conc ng/mL	CMAX	37	Y	1678	Y
CB123-201	CB123-201-102-111	102-111	102	2	Lead-in Cohort	FED	1351	Max Conc ng/mL	CMAX	37	Y	1510	Y
CB123-201	CB123-201-102-112	102-112	102	2	Lead-in Cohort	FED	3187	Max Conc ng/mL	CMAX	37	Y	1236	Y
CB123-201	CB123-201-102-113	102-113	102	2	Lead-in Cohort	FASTED	4121	Max Conc ng/mL	CMAX	37	Y	2478	Y
CB123-201	CB123-201-102-114	102-114	102	2	Lead-in Cohort	FASTED	3333	Max Conc ng/mL	CMAX	37	Y	1534	Y
CB123-201	CB123-201-102-115	102-115	102	2	Lead-in Cohort	FED	1890	Max Conc ng/mL	CMAX	37	Y	BLQ	Y
CB123-201	CB123-201-102-116	102-116	102	2	Lead-in Cohort	FED	3308	Max Conc ng/mL	CMAX	37	Y	2802	Y
CB123-201	CB123-201-102-117	102-117	102	2	Lead-in Cohort	FED	1773	Max Conc ng/mL	CMAX	37	Y	976	Y
CB123-201	CB123-201-102-118	102-118	102	2	Lead-in Cohort	FASTED	3593	Max Conc ng/mL	CMAX	37	Y	3105	Y
CB123-201	CB123-201-102-119	102-119	102	2	Lead-in Cohort	FASTED	1280	Max Conc ng/mL	CMAX	37	Y	BLQ	Y
CB123-201	CB123-201-102-120	102-120	102	2	Lead-in Cohort	FASTED	1927	Max Conc ng/mL	CMAX	37	Y	2417	Y