STATISTICAL ANALYSIS PLAN

Protocol: **PROD-124**
A Phase I Pharmacokinetic Dose-Ranging Trial of Leg Vein Imaging Drug Productocol (PROD) Administered with Plastic Bags Compared to Glass Bottles

Study Drug: Productocol (PROD)

Sponsor: CM Pharmaceuticals, Inc.

Date: 02 November, 2017

Status: **FINAL**

Prepared by:

_____ Date: _____
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1. STUDY OBJECTIVES

The objectives of this clinical trial were:

- To identify the dose of PROD, which when diluted in saline supplied in plastic bags yields similar concentration of PROD as 6.25 mg/kg of PROD diluted in the same saline supplied in glass bottles, and
- To demonstrate similar efficacy for the two dosing configurations evaluated.

2. STUDY ENDPOINTS

The endpoints of this clinical trial were:

- Concentration measurements performed with diagnostic equipment, and
- Diagnostic evaluation of the results of dosing.

3. STUDY DESIGN

This was a single-center, open-label clinical trial of PROD. All subjects received PROD.

There were two cohorts of subjects in this trial:

- Subjects in Cohort 1 received PROD administered in a plastic bag during Infusion Period 1 and PROD administered in a glass bottle during Infusion Period 2. The infusion rate of PROD was increased every 4 minutes.
- Subjects in Cohort 2 received PROD administered in a glass bottle during Infusion Period 1 and PROD administered in a plastic bag during Infusion Period 2. The infusion rate of PROD was increased every 4 minutes.

The cohorts are summarized in the following table:

Cohort	Infusion Period	PROD Administration Configuration	PROD Dose (mg/kg)
1	1	Plastic Bag	0.65
	2	Glass Bottle	1.25
2	1	Glass Bottle	1.25
	2	Plastic Bag	0.65

Evaluable subjects were those subjects in Cohorts 1 and 2 who:

- completed the imaging portion of the trial,
- had images acquired using the correct schedule and diagnostic machine settings, and
- received PROD with the proper intravenous administration equipment.

Digital diagnostic machine images of the major leg veins were acquired during each infusion period (at each flow rate) and during the intervening washout period. Digital images were acquired in the Lateral View.

The images obtained from this study were evaluated in two ways. The view clarity of the leg veins was determined for all images and each vein segment at each flow rate received one of the following three diagnostic clinical interpretations:

- normal,
- abnormal, or
- uninterpretable.

Images were obtained 4 minutes following the start of each flow rate for subjects in Cohorts 1 and 2. Flow rate escalation in Cohorts 1 and 2 occurred only after the diagnostic machine operator had determined that the images were of acceptable quality.

All series of images from each subject were reviewed by two readers blinded to PROD flow rate and administration configuration (bag/bottle). Each reader evaluated the images at each flow rate.

4. STUDY POPULATION

Healthy volunteers, comprised of men and women between the ages of 18 and 45, were considered for inclusion in this clinical trial.

5. STUDY EVALUATIONS

A time and events schedule is presented in Section 6 of this document.

5.1 Demographic and Baseline Characteristics

The following information or clinical observations were obtained within 4 hours prior to the start of PROD administration:

- Demographics
- Medical history
- Weight and height

5.2 Safety

Subjects were monitored for safety during PROD administration and for approximately 24 hours following PROD administration. Safety assessment included:

- Treatment emergent adverse events
- Clinical laboratory evaluations
- Vital signs
- Oxygen saturation
- Physical examinations
- Health Questionnaire Score

6. STUDY SCHEDULE

	Study Day 1						
	Screening & Baseline[a]	**Infusion Period 1**	**Washout Period**	**Infusion Period 2**	**Immediately Following Infusion Period 2**	**One Hour Following Infusion Period 2**	**Study Day 2**
Obtain Informed Consent	X						
Pregnancy Test**	X						
Physical Examination	X						X
Medical History and Baseline Conditions	X						
Clinical Laboratory Evaluations***	X						X
Health Questionnaire Score	X^1				X^1		
Record Temp, HR, RR, BP, O^2 Saturation (and Height and Weight on Study Day 1)	X						X
HR, BP, O^2 Saturation		X^2	X^2	X^2	X^2	X	
Administer PROD		X		X			
Acquire Digital Diagnostic Machine Images	X^3	X^3	X^3	X^3			
Record Adverse Events						X	X
Record Concomitant Medications						X	
Record Amount of PROD Administered						X	

[a] All baseline evaluations must be performed within 4 hours prior to the start of PROD administration unless otherwise indicated

** For women of childbearing potential

*** Hemoglobin, Hematocrit, WBC and differentiation, Platelets, Sodium, Potassium, Chloride, Creatinine, BUN, Albumin, Total Protein, Bilirubin (total and direct), LDH, AST, ALT, PT (or INR), PTT (or KPTT)

X^1 Prior to Infusion Period 1 and immediately after Infusion Period 2

X^2 Every 5 minutes from Minute -5 to completion of Infusion Period 2 and one hour after completion of Infusion Period 2

X^3 Minute -5, Minute -1, 4 minutes following each infusion rate increase during Infusion Period 1 and 2 (repeat acquisition as required), and every 4 minutes during the Washout Period

7. STATISTICAL METHODS

In general, summary statistics (mean, median, standard deviation, minimum and maximum) will be calculated for continuous variables, and the number and percentage of subjects in each category will be provided for categorical data.

7.1 Data Handling

Baseline is the last measurement prior to the start of PROD administration.

7.2 Subject Accountability

The number of subjects who received PROD and completed the trial will be summarized. The number of subjects who discontinued during the trial and the reasons for their early discontinuation will also be summarized.

7.3 Protocol Deviation

The number subjects with important protocol deviations, as defined by the Sponsor, will be summarized by important protocol deviation type. Important protocol deviations are those identified by the Sponsor as being in the following categories:

- Entrance criteria not met,
- Incorrect dose given,
- Withdrawal criteria met but subject not withdrawn from trial,
- Received excluded concomitant medication, and
- Other.

All protocol deviations will be listed by subject. A flag designating the Sponsor-defined important protocol deviation type will be included in this listing.

7.4 Analysis of Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, gender, race, weight, height and medical history will be presented in data listings and summarized for all subjects who received PROD using summary statistics (n, mean, standard deviation, median, minimum and maximum for age, weight, and height; n and percentages for categories of gender, race and medical history) by cohort.

7.5 Concomitant Medications

Concomitant medications will be coded to a therapeutic area using the WHO Drug Reference List (Level I and Level III). All Concomitant medications taken will be

presented in data listings for all subjects who received PROD. A separate listing will be provided for concomitant medications known to be associated with causing blood clots.

7.6 Analysis Populations

Up to 38 subjects will be enrolled to ensure at least 24 are evaluable. One investigational site was utilized. The definitions of analysis populations are:

Safety: All subjects who received PROD.

Evaluable: All subjects in Cohorts 1 or 2 who:

- completed the imaging portion of the trial,
- had images acquired using the correct schedule and diagnostic machine settings, and
- received PROD with the proper intravenous administration equipment.

7.7 Diagnostic Interpretation

Diagnostic clinical interpretation data will be summarized as percent of vein segments with normal interpretations at each flow rate and at each triggered interval and will be compared between the plastic bag and the glass bottle separately for the two readers blinded to PROD flow rate and administration configuration. For calculation of percent of vein segments with normal interpretations, the numerator will include all segments with "definitely normal" and "artifact – probably normal" interpretations and the denominator will include all segments. Diagnostic interpretation data will also be listed.

A Fisher's exact test will be used to determine if there is any difference between bag and bottle configurations in terms of diagnostic interpretation. Fisher's exact tests will also be used to see if there is any difference between the flow rates in terms of diagnostic interpretation for bags and bottles separately. A non-significant p-value for both bag and bottle configurations will provide evidence for a plateau in flow rate.

7.8 Extent of Exposure

For all subjects who received PROD, the following parameters will be summarized and listed:

- Amount of PROD administered (mg)
- Weight-based amount of PROD administered (mg/kg)

7.9 Safety Analysis

Safety data will be summarized and presented for all subjects who receive any PROD. Safety endpoints for this trial include:

- Treatment emergent adverse events

- Clinical laboratory evaluations
- Vital signs
- Oxygen saturation
- Physical examinations
- Health Questionnaire Score

Adverse Events

Adverse events will be coded using the MedDRA dictionary and will be categorized by body system and preferred term. Unique CRF verbatim terms and the MedDRA preferred terms and body systems assigned will be listed in a matching chart (See Preface A to adverse events data).

For all adverse events, a summary containing the following counts and percentages of subjects will be presented:

- the number of adverse events
- the number and percentage of subjects with at least one adverse event
- the number and percentage of subjects with serious adverse events
- the number and percentage of subjects with adverse events resulting in discontinuation of PROD
- the number and percentage of subjects with adverse events by severity
- the number and percentage of subjects who died.

Number of subjects with adverse events will be summarized by body system and preferred term.

Laboratory Evaluations

Clinical laboratory evaluations were obtained within 4 hours prior to PROD administration and on Study Day 2 and will be summarized using descriptive statistics. Laboratory test results will also be evaluated using standard reference ranges from the corresponding clinical laboratories to tabulate the occurrence of values above and below the normal reference range (See Preface B to laboratory data.). Values outside the normal range will be flagged in data listings and will be summarized in tables.

Vital Signs and Oxygen Saturation

Heart rate, blood pressure, oxygen saturation, respiration rate, and temperature were assessed on Study Day 1 prior to the start of PROD Infusion Period 1 and on Study Day 2. In addition, heart rate, blood pressure and oxygen saturation were recorded:

- Every 5 minutes from 5 minutes prior to the beginning of PROD administration (Minute -5) through the completion of Infusion Period 2
- At the end of Infusion Period 2

- One hour after the completion of Infusion Period 2

Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate), oxygen saturation measurements and the associated changes from baseline will be summarized using descriptive statistics.

All subjects who developed changes from baseline of potential clinical importance will be tabulated and flagged in the subject data listings. Criteria used will be as follows:

REFERENCE RANGES AND CRITERIA FOR BLOOD PRESSURE, HEART RATE, AND OXYGEN SATURATION VALUES OF POTENTIAL CLINICAL IMPORTANCE

Variable	Normal Reference Range	Values of Potential Clinical Importance
Systolic BP	90 – 200 mm Hg	Outside the normal reference range and change from baseline ≥ ± 20 mm Hg
Diastolic BP	60 – 120 mm Hg	Outside the normal reference range and change from baseline ≥ ± 10 mm Hg
Heart Rate	45 – 120 bpm	Outside the normal reference range and change from baseline ≥ ± 10 bpm
Oxygen Saturation	≥ 90%	< 90% and decrease from baseline ≥ 5 %

An increase/decrease from baseline of potential clinical importance will be defined as a value above/below normal reference range with an increase/decrease greater than or equal to the criteria for change.

Respiration rate and temperature will be listed.

Physical Examinations

All physical examination results will be listed for each subject.

Health Questionnaire Score

Actual total score and change from baseline scores will be summarized using descriptive statistics.

7.10 Statistical Software

All data summaries and listings will be performed using SAS® Version 9.3 or higher, under a Windows operating system.

7.11 Sample Size

No formal sample size determination was undertaken. A total of 40 subjects could be enrolled to ensure at least 24 evaluable subjects at the final concentration of PROD and image acquisition schedule.

PROGRAMMING SPECIFICATIONS

1. Required margins: at least 1.5 inches on the binding margin and at least 1 inch on all other sides. Required font: Times New Roman, 10pt. All output should have the following header at the upper left margin:

   CM Pharmaceuticals, Inc.
   Protocol PROD-124

   and the following header at the upper right margin:

   Page Number (Page n of N)
   Date (ddmmmyyyy)

   All output should have the date (date output was generated) and internal page number at the top right corner. Tables/appendices/listings should be internally paginated (i.e., page numbers should appear sequentially within each table).

   The name of the SAS program used to generate the output and the date set names used shall be displayed in the lower left/right corner on the last footnote row of each table/listing/figure:

   Data Source: ADSL, ADxx Program: xxx.sas

2. General table and listing appearance should be as follows:
   - Output titles and column headings should be in initial capital characters and bold font. For columns that display numeric variables, include "unit" in column or row heading when appropriate.
   - Data will be centered within columns when the maximum length of the data being displayed is less than or equal to the maximum width of the column heading. When the maximum length of the data being displayed exceeds the maximum width of the column heading, the data will be left justified.
   - For all tables and listings, each page of the tables and listings will have an overline at the top to represent the start of data for the page and an underline at the bottom to represent the end of data for that particular page. All other table cell borders will be hidden.
   - For tables that require an in-text version (as noted in the mocks), page orientation should be portrait so long as the table reasonably fits, cell borders should be solid and the table title should be included as a row in the table.

3. In general, data listings should be sorted by subject number within cohort.

4. Summaries will be based on scheduled timepoints (i.e., timepoints will not be slotted).

5. The mean, median and standard deviation of a set of values should be printed out to one more decimal than the raw value.
   e.g., raw: xx
   mean, median and standard deviation: xx.x
   range (minimum and maximum): xx, xx

6. All table percentages should be reported to one decimal point.

7. The following specifications apply to tables that summarize categorical data:

   - A table should be provided for each analysis appropriate for the study even if no subjects qualify for the table.

   - Percent of events should be left blank (including the parentheses) if the number of events is zero.

   - If the categories of a parameter are ordered, then all categories between the maximum possible category and the minimum category should be included, even if n=0 for a given category between the minimum and maximum level for that parameter.

   - If the categories are not ordered, then only those categories for which there is at least one subject represented should be included.

   - A missing category should be added to any parameter for which information is not available for any subjects.

8. Missing data should be represented on subject listings as 1) dashes ("-") and properly footnoted (e.g. " - = data not available") or 2) "n/a" with footnote (i.e. "n/a = not applicable"), whichever is appropriate.

9. Times should be printed in the format "HH:MM" using a 24 hour clock. "HH" represents the 2-digit hour portion of the time. "MM" represents the 2-digit minute portion of the time. Both hour and minute portions of time are zero-filled on the left if they have only one digit. Missing time portions should be represented on subject listings as dashes ("10:--" and "--:--") Times that are missing because they are not applicable for the subject should be printed as "n/a", unless otherwise specified.

10. Baseline:
    See footnotes provided on the mockups.

11. Adverse event tables will exclude adverse events with onset date and time prior to the start of PROD Infusion, but will include adverse events with unknown onset date and times.

12. In general, subject data listings should include all subjects with data. However, if a subject data listing includes only subjects who met a certain condition, i.e., subjects with serious adverse events, and there are no subjects who met that condition, then a page marker will appear indicating that no subjects met the condition for inclusion.

8. TABLES

End-of-Text Tables:

Number	Title
	Disposition, Demography and Medical History
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End-of-Text Tables:

Number	Title
	Health Questionnaire Score
Table 10	Summary of Health Questionnaire Scores

8.1 Mockups of Tables

Table 1.1

Disposition of Subjects

Disposition	All Subjects n (%)	Evaluable Population		
		All n (%)	Cohort 1 n (%)	Cohort 2 n (%)
Number of Subjects Who Received PROD	xx	xx	xx	xx
Number of Subjects Who Completed Study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Subjects Who Discontinued Early[a]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for Discontinuation				
Adverse Event Resulting in Discontinuation of PROD	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrew Consent	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Blood Clot	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[a] Includes subjects who received any PROD.

Percentages will be presented for those categories below 'Number of Subjects Who Received PROD' using the corresponding number of subjects who received PROD as the denominator. If the number of subjects who discontinued early = 0, the subcategories which report reason for discontinuation will not appear in the table.

Table 1.2

Subjects Who Did Not Complete the Study[a]

Subject	Cohort/ Age (yrs)/ Sex/ Race	PROD Administration Completed	PROD Dose Given (mg)	Date/ Day[b] of Discontinuation	Reason for Discontinuation
xxx-xxx	x xx x <text>	Yes/No	Infusion Period 1 xx.x Infusion Period 2 xx.x	ddmmmyyyy/xx	Adverse Event **(specify verbatim term from the AE page, not from the discontinuation page)** Withdrew consent – **(specify)** Lost to follow-up – **(specify)** Right-to-left cardiac shunt Other – **(specify)**

[a] Includes subjects who received any PROD.
[b] Relative to the administration of PROD. Day of administration of PROD = Day 1.

If there are no subjects that did not complete the study, a 'placeholder table' will simply state 'No subjects qualify for this table.'

Table 1.3

Summary of Important Protocol Deviations[a]

Study Population: Safety

	All Subjects (N = xx) n (%)
Protocol Followed Without Important Deviations Through Study Day 2	
Yes	xx (xx.x)
No	xx (xx.x)
Important Deviation Types:[b]	
Entrance Criteria Not Met	xx (xx.x)
Incorrect Dose Given	xx (xx.x)
Withdrawal Criteria Met but Subject not Withdrawn from Trial	xx (xx.x)
Received Excluded Concomitant Medication	xx (xx.x)
Other	xx (xx.x)

[a] As defined by the Sponsor
[b] Subjects may have more than one important protocol deviation type. (See Listing 1)

** PROGRAMMING NOTE: In-text version of this table is required.

Table 2

Demographic and Baseline Characteristics

Study Population: Safety

Characteristic	All Subjects (N = xx)	Evaluable Population		
		All (N = xx)	Cohort 1 (N = xx)	Cohort 2 (N = xx)
Age (yrs)				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Range (Min, Max)	(xx,xx)	(xx,xx)	(xx,xx)	(xx,xx)
Sex n (%)				
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race n (%)				
Caucasian	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hispanic	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Weight (kg)				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x
Range (Min, Max)	(xx,xx)	(xx,xx)	(xx,xx)	(xx,xx)
Height (inch)				
n	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x

Range (Min, Max)	(xx,xx)	(xx,xx)	(xx,xx)	(xx,xx)

** PROGRAMMING NOTE: In-text version of this table is required.

Table 3

Medical History

Study Population: Safety

Body System		All Subjects (N = xx) n (%)	Evaluable Population		
			All (N = xx) n (%)	Cohort 1 (N = xx) n (%)	Cohort 2 (N = xx) n (%)
Subjects with at Least One Abnormality		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Neurological	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
HEENT	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Heart	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lungs	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abdomen	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Musculoskeletal	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Peripheral Vascular	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Skin	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

	Abnormal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Show all categories (even if all normal).

Table 4

Concomitant Medications[a]

Study Population: Safety (N = xx)

Anatomical Area/ Therapeutic Area/ WHO Preferred Term	All Subjects n (%)	Cohort 1 n (%)	Cohort 2 n (%)
Subjects with at Least One Medication Recorded	xx (xx.x)	xx (xx.x)	xx (xx.x)
Anatomical Area	xx (xx.x)	xx (xx.x)	xx (xx.x)
Therapeutic Area	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term	xx (xx.x)	xx (xx.x)	xx (xx.x)
.			
.			
.			
Therapeutic Area			
Preferred Term			
.			

[a] Coded using the WHO Drug Reference List (Level I and III).
Note: If a subject had more than one concomitant medication in an anatomical or therapeutic area, the subject was counted once in the respective anatomical or therapeutic area total.

If no concomitant medications were reported, a 'placeholder table' will simply state 'No concomitant medications taken.'

Table 5.1

Summary of Diagnostic Interpretation – Reader 1

Study Population: Evaluable (N = xx)

Flow Rate (mL/hr)	Bag				Bottle			
	N[d]	Normal n (%)	Abnormal n (%)	Uninterpretable n (%)	N[d]	Normal n (%)	Abnormal n (%)	Uninterpretable n (%)
5	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)
10								
15								
20								

[a]p Fisher's exact test p-value for difference in diagnostic interpretation between bag and bottle configurations at 15 mL/hr flow rate < 0.05;
[b]p Fisher's exact test p-value for difference in diagnostic interpretation between the flow rates of 15 mL/hr and 20 mL/hr for bags < 0.05.
[c]p Fisher's exact test p-value for difference in diagnostic interpretation between the flow rates of 15 mL/hr and 20 mL/hr for bottles < 0.05.
[d] Number of vein segments for all evaluable patients.

Repeat this format for Table 5.2 (Summary of Diagnostic Interpretation - Reader 2).

Table 6

Exposure to PROD

Study Population: Safety (N = xx)

Parameter	Total		Bag Configuration		Bottle Configuration	
	Bag (N = xx)	Bottle (N = xx)	Infusion Period 1 (N = xx)	Infusion Period 2 (N = xx)	Infusion Period 1 (N = xx)	Infusion Period 2 (N = xx)
Amount Administered (mg)						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Range (Min, Max)	(xx,xx)	(xx,xx)	(xx,xx)	(xx,xx)	(xx,xx)	(xx,xx)
Weight-based Amount Administered (mg/kg)						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Range (Min, Max)	(xx,xx)	(xx,xx)	(xx,xx)	(xx,xx)	(xx,xx)	(xx,xx)

** PROGRAMMING NOTE: In-text version of this table is required.

Preface A

Preface to Adverse Event Table
MedDRA Body System/Preferred Term and CRF Verbatim Terms

MedDRA Body System	MedDRA Preferred Term	CRF Verbatim Term

Table 7.1.1

Summary of Adverse Events[a]

Study Population: Safety

	All Subjects (N = xx) n (%)	**Cohort 1 (N = xx) n (%)**	**Cohort 2 (N = xx) n (%)**
Number of Subjects	xx	xx	xx
Number of Adverse Events	xx	xx	xx
Subjects with Adverse Event(s)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Related to PROD	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Serious Adverse Event(s)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Adverse Event(s) that Resulted in Discontinuation of PROD	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Adverse Events by Severity[b]			
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
Life-Threatening	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing **only to appear if there is missing severity**	xx (xx.x)	xx (xx.x)	xx (xx.x)

[a] Includes all adverse events reported after start of PROD administration.
[b] If a subject experienced more than one adverse event, the subject was counted once at the maximum severity.

Repeat format for Table 7.1.2 Summary of Adverse Events Related to PROD

Remove line "Related to PROD" under Subjects with Adverse Event(s) row and change [a] footnote to:

[a] Includes all adverse events reported after start of PROD administration that are considered definitely, probably, or possibly related to PROD.

Table 7.2.1

Adverse Events[a] by Body System

Study Population: Safety

MedDRA Body System[b] Preferred Term[c]	All Subjects (N = xx) n (%)	Cohort 1 (N = xx) n (%)	Cohort 2 (N = xx) n (%)
Subjects with Adverse Event(s)[d]	xx	xx	xx
Body System	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…
Body System	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term	xx (xx.x)	xx (xx.x)	xx (xx.x)

[a] Includes all adverse events reported after start of PROD administration.
[b] Subjects who had more than one event within a body system were counted once.
[c] Subjects who had more than one event assigned to the same preferred term were counted once.
[d] Subjects who had more than one event were counted once.

Repeat format for Table 7.2.2 Adverse Events by Body System Related[a] to PROD
Change [a] footnote to:
[a] Includes all adverse events reported after start of PROD administration that are considered definitely, probably, or possibly related to PROD.

** PROGRAMMING NOTE: In-text version of Table 7.2.2 is required.

Table 7.3.1

Adverse Events[a] by Body System and Severity

Study Population: Safety

MedDRA Body System[b] Preferred Term[c]	All Subjects (N = xx) Severity				
	Total n (%)	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Life-threatening n (%)**
Subjects with Adverse Event(s)[d]	xx	xx	xx	xx	xx
Body System	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…	…
Body System	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[a] Includes all adverse events reported after start of PROD administration.
[b] Subjects who had more than one event within a body system were counted once.
[c] Subjects who had more than one event assigned to the same preferred term were counted once.
[d] Subjects who had more than one event were counted once, and the occurrence with the maximum severity was counted.

Repeat format for Table 7.3.2 Adverse Events Related to PROD by Body System and Severity
Change [a] footnote to:

[a] Includes all adverse events reported after start of PROD administration that are considered definitely, probably, or possibly related to PROD.

Table 7.4

Serious Adverse Events by Subject

Subject	Cohort Age Sex Race	MedDRA Body System MedDRA Preferred Term CRF Verbatim Term	Onset Time[a] Relative to PROD (D:H:M)	Duration (D:H:M)	Severity	Relationship to PROD	Action Taken
xxx-xxx	1 60 Male White	Cardiovascular System Bradycardia Slow Heart Rate	0:00:48	00:00:25	Moderate	Possibly	None
xxx-xxx				ongoing			

[a] Relative to the start of PROD administration. Negative times indicate occurrence prior to the start of PROD administration.

Duration (D:H:M): D = Days; H = Hours; M = Minutes.

Sort by subject and onset time relative to PROD.

Table 8.1

Summary of Clinical Laboratory Results

Study Population: Safety (N = xx)

Laboratory Parameter		Baseline[a]				Scheduled Timepoint				Change from Baseline			
Scheduled Timepoint	N	Mean	SD	Median	(Min, Max)	Mean	SD	Median	(Min, Max)	Mean	SD	Median	(Min, Max)
Sodium (mmol/L)													
Baseline[a]	xx	xx.x	xx.x	xxx	(xxx, xxx)								
Study Day 2	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
Potassium (mmol/mL)													
Baseline[a]	xx	xx.x	xx.x	xxx	(xxx, xxx)								
Study Day 2	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
…													
PTT (sec)													

[a] Within 4 hours prior to the start of PROD administration.

Note: Summary statistics for change from baseline include those subjects with a baseline and a Study Day 2 value.

Table 8.2

Clinical Laboratory Values
Relationship of Laboratory Values to Normal Reference Range - Serum Chemistry, Hematology and Coagulation

Study Population: Safety (N = xx)

			Study Day 2			
Laboratory Parameter	**N[a]**	**Baseline[b]**	**Low n (%)**	**Normal n (%)**	**High n (%)**	**Missing[c] N**
Sodium (mmol/L)						
	xx	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
		Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
		High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
		Missing	xx	xx	xx	xx
Potassium (mmol/L)	xx	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
		Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
		High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
		Missing	xx	xx	xx	xx
…						
PTT (sec)						

[a] Includes subjects with both baseline and Study Day 2 values. Used as the denominator for percentages.
[b] Within 4 hours prior to the start of PROD administration
[c] Includes subjects with a baseline value but no Study Day 2 value.

See Preface B for normal reference ranges and criteria for identifying values of potential clinical importance.

Table 9.1

Vital Signs - Systolic Blood Pressure (mm Hg)

Study Population: Safety (N = xx)

Cohort[a]	Scheduled Timepoint	N	Baseline[b] Mean	SD	Median	(Min, Max)	Scheduled Timepoint Mean	SD	Median	(Min, Max)	Change from Baseline Mean	SD	Median	(Min, Max)
1	Screening	xx	xx.x	xx.x	xxx	(xxx, xxx)								
	-5 min	xx	xx.x	xx.x	xxx	(xxx, xxx)								
	0 min	xx	xx.x	xx.x	xxx	(xxx, xxx)								
	Baseline[b]	xx	xx.x	xx.x	xxx	(xxx, xxx)								
	+5 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	+10 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	+15 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	+20 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	+25 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	+30 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	+35 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	+40 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	+45 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	+105 min	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
	Study Day 2	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)
2														

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.
[b] Baseline is the last value prior to the start of PROD.
Note: Summary statistics at each scheduled timepoint include those subjects with a baseline value and a value at the scheduled timepoint.

Repeat this format for Table 9.2 (Vital Signs - Diastolic Blood Pressure (mm Hg)), Table 9.3 (Vital Signs - Heart Rate (beats/min)), and Table 9.4 (Oxygen Saturation (%)).

Table 9.5

Vital Signs – Changes of Potential Clinical Importance from Baseline

Study Population: Safety (N = xx)

Parameter (Reference Range) Criteria for Change	Scheduled Timepoint	All Subjects N[b]	All Subjects n(%)	Cohort 1[a] N[b]	Cohort 1[a] n(%)	Cohort 2[a] N[b]	Cohort 2[a] n(%)
Systolic Blood Pressure (90-200 mm Hg)							
Increase >= 20 mm Hg	Postdose						
	+5 min	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
	…						
	+105 min	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
	Study Day 2	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
	Any Timepoint[c]	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)
Decrease >= 20 mm Hg							
Diastolic Blood Pressure (60-120 mm Hg)							
Increase >= 10 mm Hg							
Decrease >= 10 mm Hg							
Heart Rate (45-120 bpm)							
Increase >= 10 bpm							
Decrease >= 10 bpm							

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.
[b] Includes subjects with a baseline value and at least one postdose value for the corresponding variable. Used as the denominator for percentages.
[c] Includes all scheduled timepoints.

Criteria for changes of potential clinical importance are as follows:
Systolic blood pressure above/below normal reference range (90 to 200 mm Hg) and increase/decrease >= 20 mm Hg
Diastolic blood pressure above/below normal reference range (60 to 120 mm Hg) and increase/decrease >= 10 mm Hg
Heart rate above/below normal reference range (45 to 120 bpm) and increase/decrease >= 10 bpm

Table 10

Summary of Health Questionnaire Scores

Study Population: Safety (N = xx)

Scheduled Timepoint	N	Baseline				Scheduled Timepoint				Change from Baseline			
		Mean	SD	Median	(Min, Max)	Mean	SD	Median	(Min, Max)	Mean	SD	Median	(Min, Max)
Baseline	xx	xx.x	xx.x	xxx	(xxx, xxx)								
Postdose	xx	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)	xx.x	xx.x	xxx	(xxx, xxx)

Note: Summary statistics for change from baseline at each scheduled timepoint include those subjects with a baseline value and a value at the scheduled timepoint.

9. LISTINGS

Listings:

Number	Title
	Disposition, Demography and Medical History
Listing 1	Protocol Deviations
Listing 2	Demographics and Baseline Characteristics
Listing 3	Medical History
Listing 4	Concomitant Medications
	Exposure
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Listing 7	Clinical Laboratory Values – Serum Chemistry, Hematology and Coagulation
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Listing 8.1	Vital Signs (Blood Pressure and Heart Rate) and Oxygen Saturation
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	Physical Examination
Listing 9	Physical Examination
	Health Questionnaire
Listing 10	Health Questionnaire Scores

9.1 Mockups of Listings

Listing 1

Protocol Deviations

Subject	Cohort[a]	Description	Important Deviation[b]	Important Departure Type
xxx-xxx	1	<text>	Yes, No	Entrance criteria not met Incorrect dose given Withdrawal criteria met but subject not withdrawn from trial Received excluded concomitant medication Other

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.
[b] As defined by Sponsor.

Listing 2

Demographics and Baseline Characteristics

Subject	Cohort[a]	Informed Consent Date	Date of Birth	Age (yrs)	Sex	Race	Weight (kg)	Height (inch)
xxx-xxx	1	ddmmmyyyy	ddmmmyyyy	xx.x	Male Female	Caucasian Black Hispanic Asian Other, specify	xx.x	xx.x

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.

Listing 3

Medical History

Subject	Cohort[a]	Body System	Result	Description
xxx-xxx	1	Neurological	Abnormal	Description of any abnormality
		HEENT	Normal	
		Heart		
		Lungs		
		Abdomen		
		Musculoskeletal		
		Peripheral Vascular		
		Skin		
		Other		
xxx-xxx				

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.

List all body systems for all subjects even if the results are normal.

Listing 4

Concomitant Medications[a]

Subject/ Cohort[b]	Anatomical Area/ Therapeutic Area/ WHO Preferred Term	Medication as per CRF (Generic Name)	Indication	Dose/ Unit/ Route	Start Day[c] (D:H:M)
xxx-xxx/1	<text>/ <text>/ <text>	Verbatim as entered on CRF. Generic name in parenthesis.	<text>	xxxx/ xxxx/ xxxx	xx:xx:xx

[a] Coded using the WHO Drug Reference List (Level I and III)
[b] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.
[c] Relative to the start of PROD administration; D:H:M : D=Days; H=Hours; M=Minutes

Listing 5

PROD Administration

Subject/ Cohort[a]	Weight (kg)	Infusion Period/ Configuration	Amount Administered (mg)	Amount Administered (mg/kg)	Date	Start Time	Stop Time
xxx-xxx/1	xxx	1/Bag	xx.x	xx.x	ddmmmyyyy	hh:mm	hh:mm
		2/Bottle	xx.x	xx.x		hh:mm	hh:mm
xxx-xxx	xxx						

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.

Listing 6

Adverse Events

Subject	Cohort[a] Age Sex Race	MedDRA Body System MedDRA Preferred Term CRF Verbatim Term	Onset Time (HH:MM)	Onset Time[b] Relative to PROD (D:H:M)	Duration (D:H:M)[c]	Severity	Relationship to PROD	Action Taken
xxx-xxx	1 60 Male White	Cardiovascular System Bradycardia Slow Heart Rate	12:30	0:00:48	00:00:25	Moderate	Possibly	None
xxx-xxx					ongoing			

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.
[b] Relative to the start of PROD administration. Negative times indicate occurrence prior to the start of PROD administration.
[c] Duration (D:H:M): D = Days; H = Hours; M = Minutes.

Sort by subject and onset time relative to PROD.

Preface B

Preface of Clinical Laboratory Reference Ranges and Criteria for Values of Potential Clinical Importance

Laboratory Parameter Laboratory Name	Effective Date	Race	Sex	Age Range	Normal Reference Range	Unit	Values of Potential Clinical Importance[a]
			Male	12-58	39 - 54		
				59-99	37 - 51		
			Female	All Ages	34 - 48		

[a] Values that are outside the normal reference range and meet the criteria for values of potential clinical importance.
n/a = not applicable

This preface will contain all laboratory parameters collected for this study.

Listing 7

Clinical Laboratory Values - Serum Chemistry, Hematology and Coagulation

Demographic Profile	Laboratory Parameter (Unit)	Baseline	Study Day 2	Laboratory Name(s)
Subject: xxx-xxx	Study Dates:	ddmmmyyyy	ddmmmyyyy	
Cohort: 1				
Age (yrs): xx	Sodium (mmol/L)	xx.x	xx.x L	<text>
Sex: Male	Potassium (mmol/L)	xx.x	xx.x L	<text>
Race: Caucasian				
Weight (kg): xxx.x				
	…			
	PTT (sec)	xx.x	xx.x	<text>

L = below normal reference range
H = above normal reference range
- = lab test not performed

See Preface B for normal reference ranges and the criteria for identifying values of potential clinical importance.

List all parameters that should have been evaluated.

Listing 8.1

Vital Signs (Blood Pressure and Heart Rate) and Oxygen Saturation

Subject	Cohort[a]	Scheduled Timepoint	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)		Heart Rate (beats/min)		Oxygen Saturation (%)	
			Value	Change[b]	Value	Change[b]	Value	Change[b]	Value	Change[b]
xxx-xxx	1	Screening	xx.x	n/a	xx.x	n/a	xx.x	n/a	xx.x	n/a
		-5 min	xx.x	n/a	xx.x	n/a	xx.x	n/a	xx.x	n/a
		0 min	xx.x	n/a	xx.x	n/a	xx.x	n/a	xx.x	n/a
		Baseline[c]	xx.x	n/a	xx.x	n/a	xx.x	n/a	xx.x	n/a
		+5 min								
		+10 min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
		+15 min								
		+20 min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
		+25 min								
		+30 min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
		+35 min								
		+40 min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
		+45 min								
		+105 min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
		Study Day 2								

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.
[b] Change from baseline.
[c] Baseline is the last value prior to the start of PROD.
I or D = Increase or decrease from baseline of clinical importance based on the criteria specified below:
Systolic blood pressure above/below normal range (90 to 200 mm Hg) and increase/decrease >= 20 mm Hg
Diastolic blood pressure above/below normal range (60 to 120 mm Hg) and increase/decrease >= 10 mm Hg
Heart Rate above/below normal range (45 to 120 bpm) and increase/decrease >= 10 bpm
Oxygen Saturation <90% and decrease >= 5%
n/a = not applicable
- = missing

Listing 8.2

Vital Signs (Respiration Rate and Temperature)

	Cohort[a]	Scheduled Timepoint	Respiration Rate (breaths/min)		Temperature (°C)	
			Value	Change[b]	Value	Change[b]
xxx-xxx	1	Baseline	xx.x	n/a	xx.x	n/a
		Study Day 2	xx.x	xx.x	xx.x	xx.x
xxx-xxx						

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.
[b] Change from baseline.

n/a = not applicable

Listing 9

Physical Examination

Subject	Cohort[a]	Body System	Baseline	Study Day 2
xxx-xxx	1	Neurological	Normal <text> Abnormal <text>	Normal <text> Abnormal <text>
		HEENT		
		Heart		
		Lungs		
		Abdomen		
		Musculoskeletal		
		Peripheral Vascular		
		Skin		
		Other		

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.

If explanatory text is present in the PE database, then concatenate the text with the label "Normal" or "Abnormal".

Listing 10

Health Questionnaire Scores

Subject	Cohort[a]	Baseline Score	Postdose Score	Change from Baseline Score
xxx-xxx	1	xx	Xx	xx
xxx-xxx				

[a] Cohort 1 Sequence: Bag in Infusion 1 / Bottle in Infusion 2, Cohort 2 Sequence: Bottle in Infusion 1 / Bag in Infusion 2.