CHEMICAL PHARMACEUTICAL AND BIOLOGICAL DATA

Introduction

This Clinical Trial Application presents information relating to [18F]ABC123 Injection containing 10µg/ml ABC123, 150MBq/ml at reference date and time.

2.2.1.S DRUG SUBSTANCE

2.2.1.S.1 General Information

2.2.1.S.1.1 Nomenclature

INN Name	Not yet assigned
Chemical Name (IUPAC)	*The chemical name would be provided*
Code Name	[18F]ABC123 sodium salt
Other names	Not applicable

2.2.1.S.1.2 Structure

Structural Formula	The chemical structure would be provided
Molecular Formula	The molecular formula would be presented.
Molecular Weight	342.6g/mol
Chirality/Stereochemistry	ABC123 is a single stereoisomer with the (2S) configuration.

2.2.1.S.1.3 General Properties of the non-radioactive analogue ABC123 sodium

As ABC123 is the nonradioactive analogue of [18F]ABC123, the physical properties of [18F]ABC123 will be the same as those reported.

Description	A yellow crystalline solid.
pH and pKa	pKa of 2.37.
Solubility	The solubility of ABC123 sodium salt in water at 20°C is approximately 35 mg/mL. Aqueous solubility is unaffected by pH in the range 1-8.
Hygroscopicity	ABC123 is not considered to be hygroscopic. No increase in moisture content was seen following storage at 25°C/90% RH, for 2 weeks.
Crystal Form	There is only one known crystalline form of ABC123.

Nuclear properties of the radioisotope fluorine-18	
Half-life	109.8 minutes
Principal mode of disintegration	Positron (β) decay; 96.7%
Principal gamma radiation	0.511 MeV; 193.4% emission

2.2.1.S.2 Manufacture

2.2.1.S.2.1 Manufacturer(s)

The drug substance, AB1234, is manufactured in accordance with Good Manufacturing Practice at the following facility:

Company Name	ContractSynth PET Facility
Street address	1 Old Street
Town	Sometown
Country	Anywhere

2.2.1.S.2.2 Description of Manufacturing Process and Process Controls

Introduction

The drug product is manufactured using a proprietary automated synthesiser. During the manufacture of ABC123 (18F) Injection, neither the drug substance nor the intermediate in its synthesis are isolated or tested at any time.

Synthetic route

The drug substance, [18F]ABC123 is synthesised from the Final Intermediate PQR 456

in two steps. The Final Intermediate is reacted with [18F]fluoride to give the compound

[18F]PQR789 which is then, without being isolated, treated with hydrochloric acid

to remove protecting groups. The resulting drug substance is purified by preparative HPLC.

Description of process

The [18F]fluoride is obtained by the irradiation of ^{18}O-enriched water with protons accelerated in a cyclotron according to the following reaction:

$^{18}O(p,n)18F$

The irradiated water is transferred to the fluoride loading vessel on the synthesiser. The

incoming radioactivity is measured and recorded in the batch records.

The radioactivity is trapped on a pre-conditioned single use anion exchange column cartridge (QMA). The 18O-enriched water is recovered and takes no further part in the synthesis. The [18F]fluoride is eluted from the cartridge into the reaction vessel with a 0.15 M solution of tetrabutylammonium bicarbonate in aqueous acetonitrile. The fluoride recovery from the cartridge has been shown during manufacturing development to be >99%.

The reaction vessel is heated under a combined flow of inert gas and a vacuum in order to dry the [18F]fluoride.

The PQR 456 in DMSO solution is introduced into the reaction vessel and heated to give [18F]PQR789. The decay corrected yield from this step has been shown during manufacturing development to be approximately 65-70%.

An aliquot of 4 M hydrochloric acid is added to the reaction vessel and heated to convert

[18F]PQR789 into the crude drug substance [18F]ABC123.

The solution of crude [18F]ABC123 drug substance is diluted with an aliquot of aqueous ethanol prior to injection onto a preparative HPLC column for purification of the drug substance. The mobile phase is prepared at the PET centre according to a Master Formula. The preparative HPLC method is isocratic with a flow rate of 5 ml/minute. The fraction containing the drug substance molecule is identified by a radioactive detector response at an expected retention time, passed through single use solvent exchange cartridges, which retain the drug substance, and the waste is discarded. The

cartridges are rinsed with water for injection. The purified drug substance is eluted from the cartridges into the Product collection vial with, successively, ethanol and water for injection.

Figure 1 Flow Diagram for the Synthesis of [18F]ABC123

This would be included

2.2.1.S.2.3 Control of Materials

The [18F]fluoride has a half-life of ~110 minutes so that analysis before use is not practical. Control of this material is provided by the analysis of the 18O-enriched water by the supplier and the analysis of the final drug product ABC123 (18F) Injection.

The production of the [18F]fluoride is carried out by irradiating 18O-enriched water with a proton beam produced in a cyclotron in order to cause the nuclear reaction: 18O(p,n)18F.

The radionuclidic impurities from the [18F]fluoride solution are tested for according to the

schedule at the PET manufacturing site. The production of [18F]fluoride has been validated by the manufacturer according to their local procedures.

The mode of disintegration of fluorine-18 is β+ decay (96.7%) and orbital electron capture

(3.3%). The principal gamma radiation is 0.511 MeV (193.4% emission).

The Final Intermediate is supplied in a reagent vial as a solution in DMSO. Batches are released according to the specification given in Table 3. The vials will be stored at 25 °C

(15 °C to 30 °C) and protected from light.

Table 3 Specification for PQR456 in DMSO

Tests	Analytical Methods	Acceptance criteria
Description		
Appearance	Visual inspection	Yellow solution
Identification		
Identification by IR	IR spectroscopy	conforms
Identification by HPLC	HPLC	corresponds
Assay	HPLC	27.0 to 31.0 mg/ml
Related substances	HPLC	NMT 7.00% area

2.2.1.S.2.4 Controls of Critical Steps and Intermediates

The crude reaction mixture is purified by preparative HPLC. The product peak is identified by its retention time and comparison with a representative chromatogram contained in the Master Formula.

2.2.1.S.2.5 Process Validation and/or Evaluation

The preparation of the drug product ABC123(18F) Injection from PQR456 is a

continuous process and the drug substance [18F]ABC123 is not isolated or tested at any time. Evaluation of the whole process is considered in section 2.1.P.3.5. No information yet available.

2.2.1.S.2.6 Manufacturing Process Development

Non-clinical studies were carried out using the non-radioactive analogue of the drug substance.

2.2.1.S.3 Characterisation

2.2.1.S.3.1 Elucidation of Structure and Other Characteristics

The short half-life and very low concentrations of [18F]ABC123 preclude direct structural

characterisation of the drug substance. The following describes characterisation of the nonradioactive (19F) analogue and provides evidence of the identity of the drug substance. The route of synthesis presented in Figure 1 and the spectroscopic studies performed, (Figures 2-6) are consistent with the assigned chemical structure.

Elemental Analysis

The elemental analysis results are in agreement with theoretical values.

Table 1 Elemental Analysis of ABC123 (Batch R1234/01/1)

Molecular Formula		
Element	% Theoretical	% Found
C H N	61.4 5.8 7.9	61.1 5.7 7.6
Cl	10.0	9.9
F	5.4	5.4

Infrared Spectroscopy

The infrared spectroscopic data are consistent with the chemical structure of ABC123 by assignment of band maxima to the functional groups of the molecule. The IR spectrum is presented in Figure 2.

IR Spectrum

Wave number (cm-1)	Vibrational Assignments
3228	NH stretch (amide)
3100-3000	Aryl CH stretches , OH stretch
2995-2850	Alkyl CH stretches
2800-2400	NH+stretch
1716	Amide I (α-halogenated lactam)
1659	Amide I (alkyl secondary amide),
1626, 1608	C=C, C=N stretches(aromatics)
1585	Asymmetric CO2 - stretch
1567	Amide II (alkyl amide)
1524, 1502	C=C, C=N stretches(aromatics), NH deformation (amine)
1455, 1428	CH2deformation (ether)
1406	symmetric CO2 - stretch
1400- 1250	NH deformation (amine), Amide III, C-O-H deformation (phenol)
1227 / 1211	asymmetric C-O-C stretch (alkyl-aryl ether), C-C-O stretch (phenol)
1200-1090	Aryl-F, CF2stretches
1075	symmetric C-O-C stretch (alkyl-aryl ether)
900-750	C-H out-of-plane deformation (aromatic)

Figure 2 Infrared Spectrum of a Mineral Oil Mull of ABC123 (Batch R1234/01/1)

[The IR spectrum would be presented.]

NMR Spectroscopy

The signals from a proton nuclear magnetic resonance (^{1}H-NMR) spectrum were assigned to the protons in the molecule. The signals from a carbon nuclear magnetic resonance (^{13}C-NMR) spectrum were assigned to the carbons present in the molecule. All spectra obtained were consistent with the structure of ABC123. The ^{1}H-NMR and ^{13}C-NMR spectra and their assignments are presented in Figures 3 and 4 respectively.

1H-NMR shifts

Atom Number	1H Chemical Shift	No. of Hs	Multiplicity	J (Hz)
34	2.65	3	doublet	4.6
30	4.34	2	singlet	-
25	6.49	1	multiplet	8.1, 2.2
26	7.10	1	triplet	8.1
7	7.26	1	doublet	8.8
27	7.26	1	multiplet	8.1, 2.2
38	7.39	1	doublet	8.8
23	7.40	1	triplet	2.2
10	7.47	1	doublet	2.4
42	7.58	1	multiplet	8.1, 6.8, 1.2
8	7.60	1	multiplet	8.8, 2.4
41	7.68	1	multiplet	8.1, 6.8, 1.2
37	7.75	1	doublet	8.8
40	7.90	1	doublet	8.1
33	7.92	1	quartet	4.6
19	8.14	1	doublet	3.4
43	8.29	1	doublet	8.1
21	9.15	1	singlet	-
14	9.56	1	multiplet	-
4	11.93	1	triplet	2.9

Figure 3 400 MHz ^{1}H-NMR Spectrum of ABC123 (Batch R1234/01/1) in 2% w/v DCl in D_2O

13C-NMR

Chemical Shift (ppm)	**Position**	**# of Carbons**
170	C26	1
152	Aryl – CH	1
148	Aryl – CH	1
148	Aryl – CH	1
140	Vinyl –C	1
134	Vinyl –C	1
133	Aryl –C	1
129	Vinyl –C	1
123	Vinyl –CH	1
122	Vinyl –CH	1
74	C3	1
57	-C	1
50	-C	1
47	-C	1
38	-CH	1
37	-CH	1
37	-CH2	1
35	-CH2	1
32	-CH2	1
31	-CH2	1
30	-CH2	1
28	-CH2	1
21	-CH2	1
21	-CH3	1
19	-CH3	1
17	-CH3	1

Figure 4 ^{13}C-NMR Spectrum of ABC123 (Batch R1234/01/1) in 2% w/v DCl in D_2O

[The ^{1}H-NMR spectrum would be presented.]

Mass Spectrometry

The electrospray mass spectrum, presented in Figure 5 indicates the spectrum is consistent with the proposed structure.

Figure 5 Electrospray Product Ion Mass Spectrum of ABC123 (Batch R1234/01/1)

[The mass spectrum and a table of assignments would be presented.]

2.2.1.S.3.2 Impurities

The drug substance is not tested prior to preparation of the drug product. Potential impurities are the starting material and intermediates during the preparation of PQR456 and PQ456 itself. Typical levels have been determined from the synthesis of the non-radioactive [19F] analogue.

Table 2 Potential Process Impurities and Degradation Products for [19F]ABC123

Code Name	**Structural Formula**	**Notes**	**Typical Level Observed**
XYZ123	To be included	Starting material	0.44%
XYZ456	To be included	Starting material	0.2%
PQR456	To be included	Intermediate, degradant,	0.11%
LM1122	To be included	Degradant	0.25%
Palladium		Catalyst	2.3ppm
Toluene		Solvent	600ppm
Ethanol		Solvent	2500ppm

2.2.1.S.4 Control of Drug Substance

2.2.1.S.4.1 Specification

As the synthesis of [18F] ABC123 substance and its formulation into drug product are parts of a continuous process, specifications and associated testing are set only for the drug product.

2.2.1.S.4.2 Analytical Procedures

Not applicable

2.2.1.S.4.3. Validation of Analytical Procedures

Not applicable

2.2.1.S.4.4 Batch Analyses

Not applicable

2.2.1.S.4.4 Justification of Specification

Not applicable

2.2.1.S.6 Container Closure System

Not applicable

2.2.1.S.7 Stability

Not applicable

2.2.1.P DRUG PRODUCT

2.2.1.P.1 Description and Composition of the Drug Product

Description

Each vial contains 10ml of [18F]ABC123 Injection 150MBq/ml at reference date and time. The drug product is contained in a type I glass vial sealed with a type I synthetic rubber closure.

Composition

The complete statement of the components and quantitative composition of [18F]ABC123 Injection is given below in Table 6.

Table 6 Composition of [18F]ABC123 Injection

Component	Quantity (Unit/ml)	Function	Reference to Standard
[18F] ABC123	150MBq at reference date and time	Drug substance	N/A
Ethanol	0.5ml	Solubiliser	PhEur
Water for Injection	To 1ml	Solvent	PhEur

2.2.1.P.2 Pharmaceutical Development

The drug substance [18F]ABC123 is provided in the form of an aqueous ethanol solution and is not isolated or tested following synthesis. It is administered by intravenous bolus injection following dilution with 0.9% Sodium Chloride Injection.

2.2.1.P.3 Manufacture

2.2.1.P.3.1 Manufacturer(s)

The manufacture of [18F]ABC123 Injection is conducted in accordance with Good Manufacturing Practice at the following facility:

Company Name	WeMakeForU Clinical Imaging Centre
Street address	The Avenue
Town	AnyTown
Country	SomeWhere

2.2.P.3.2 Batch Formula

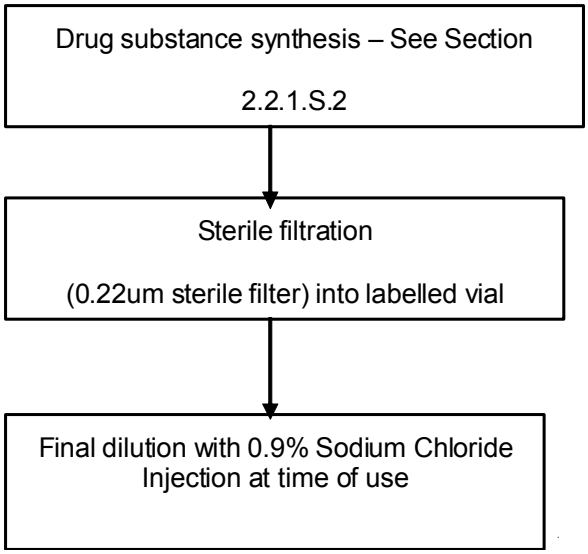
Not applicable

2.2.1.P.3.3 Description of Manufacturing Process and Process Controls

The drug substance ([18F]ABC123) dissolved in aqueous ethanol is sterile filtered (0.22um) and aseptically dispensed. The sterile filter used during production is integrity tested after filtration as part of the manufacturing procedure. An appropriate aliquot is further diluted with 0.9% Sodium Chloride Injection in a sterile syringe for immediate administration.

The flow diagram of the manufacturing process is given in Figure 7.

Figure 7 Flow Diagram of the Manufacturing Process



2.2.1.P.3.4 Controls of Critical Steps and Intermediates

There are no isolated intermediates.

2.2.1.P.3.5 Process Validation and/or Evaluation

The manufacture of [18F]ABC123 Injection has been evaluated in three development batches. The bioburden of these batches have been assessed prior to the transfer through the sterile filter. The limit of NMT 5 CFU/ml was used instead of the general limit for bioburden for acceptance of sterilisation by filtration of NMT 10 CFU/100 ml due to a total batch volume of 50 ml and a detection limit of 1 CFU/ml. Challenge of the filter membrane with minimum 10^7 CFU/cm^2 of filter area (2.8 cm^2) demonstrated that the membrane is capable of retaining this bacterial load suspended in the non-radioactive analogue.

Evaluation of the aseptic manufacture has been performed on the three development batches. Media fill validation of the aseptic dispensing system has been performed successfully at the manufacturing sites

2.2.1.P.4 Control of Excipients

2.2.1.P.4.1 Specifications

The following excipients used in the manufacture of the finished product are required to comply with the specifications listed below.

Excipient	**Specification**
Ethanol	Ph Eur
Water for Injection	Ph Eur

2.2.1.P.4.5 Excipients of Human or Animal Origin

No excipients are of human or animal origin.

2.2.1.P.4.6 Novel Excipients

None involved.

2.2.1.P.5 Control of Drug Product

2.2.1.P.5.1 Specification(s)

Clinical trial batches will meet the following specification at release.

Table 6 [18F]ABC123 Injection Specifications

Test	**Specification**
Identification	Concordant with reference standard
Appearance	Clear, colourless, free from particles
Radioactive half-life Gamma energy	109.7 min ± 5% Concordant with F-18 energy spectrum
Radiochemical Purity	Not less than 90%
Nominal activity	90 to 110% of 150 MBq/ml at the date and time stated on the label
Content of ABC123	Not more than 1 µg /ml
pH	4.5 – 8.5
Bacterial Endotoxins	Not more than 175 EU (endotoxins of gram negative bacterial origin)
Sterility Testing	Complies with Ph. Eur.

Due to the short half-life (109.77 min) of fluorine-18 it is not possible to test [18F]ABC123 Injection prior to administration hence the following tests are conducted prior to dilution; identity, appearance, radionuclidic identity (radioactive half-life and gamma energy), radiochemical purity, impurities (chemical), pH and bacterial endotoxins. Sterility testing is completed after administration of the product

2.2.1.P.5.2 Analytical Procedures

The methods used to control the drug substance are summarised below. In the course of ongoing development, analytical methods will continue to be optimised and revised methods implemented and appropriately validated.

Appearance

The product is visually inspected through lead glass.

Identification by HPLC

The identity of the drug substance is verified using HPLC and comparing the retention time of the main peak in the radio chromatogram with the retention time of an ABC123 standard in a UV chromatogram.

Radionuclidic identity by half life determination and gamma energy

The radionuclidic identity of fluorine-18 is determined by measuring the radioactivity and calculating the half life from the decay rate as described in the Ph.Eur. monograph for radiopharmaceutical preparations and by gamma-ray spectroscopy. The gamma-ray spectrum is examined over the energy range of 0-1.5 MeV. The presence of F-18 is confirmed by a photopeak at 511 keV.

Radiochemical purity

The radiochemical purity is determined by reverse phase HPLC using the method as described for determination of content of ABC123 with radio detection.

Nominal activity

The nominal activity (label claim) is defined as 150 MBq/ml at reference time. The date and time for the nominal activity is calculated by measurement of the radioactive concentration using an ionisation chamber.

Content of ABC123

The concentration of ABC123 is determined by HPLC

pH

The pH of the product is measured using a pH meter equipped with a combined glass/reference electrode or by using pH indicator paper. The pH meter is calibrated against certified calibration buffers.

Bacterial endotoxins

Testing of bacterial endotoxins conforms to both USP and Ph.Eur. monographs on parenteral products.

Sterility

The sterility testing conforms to both USP and Ph.Eur. monographs on parenteral products.

2.2.1.P.5.3. Validation of Analytical Procedures

All non pharmacopoeial analytical methods have been qualified for selectivity, precision and accuracy and are considered as suitable for use.

2.2.1.P.5.4 Batch Analyses

Batch details and batch analysis data are provided in Table 7 for three batches of [18F]ABC123 Injection.

Table 7 Batch Analysis Data

Date of Manufacture		May 2010	May 2010	May 2010
Site of Manufacture		WeMakeForU AnyTown	WeMakeForU AnyTown	WeMakeForU AnyTown
Test	Acceptance Criteria			
Identification	Concordant with reference standard	Conforms	Conforms	Conforms
Appearance	Clear, colourless, free from particles	Conforms	Conforms	Conforms
Radioactive half-life	109.7 min ± 5%	107	110	106
Gamma energy	Concordant with F-18 energy spectrum	Conforms	Conforms	Conforms
Radiochemical Purity	Not less than 90%	99 %	97 %	98 %
Nominal activity	90 to 110% of 150 MBq/ml at the date and time stated on the label	106%	102%	97%
Content of ABC123	Not more than 1 µg /ml	0.10	0.11	0.20
pH	4.5 – 8.5	6.91	7.31	6.97
Bacterial Endotoxins	Not more than 175 EU (endotoxins of gram negative bacterial origin)	14	17	8.8
Sterility Testing	Complies with Ph. Eur.	Pass	Pass	Pass

2.2.1.P.5.5 Characterisation of Impurities

No additional impurities have been detected.

2.2.1.P.5.6 Justification of Specification(s)

The specification applied is considered appropriate for the stage of development. The impurity profile is acceptable based on the dose to be administered.

2.2.1.P.6 Reference Standards or Materials

Batch Number		R1234/01/1
Batch Size (kg)		1.15
Place of Manufacture		ContractSynth SomeTown
Date of Manufacture		Jan 2009
Use		Nonclinical/Clinical
Description	Yellow crystalline solid	Yellow crystalline powder
Identification ABC123 by IR	The spectrum of the sample is concordant with that of the ABC123 authentic material.	Conforms
ABC123 content by HPLC (% w/w)	Greater than 97	99.2
Drug-related impurities content by HPLC, (% area) XYZ123 XYZ456 PQR456 LM1122 Any unqualified impurity Total	 Not greater than 0.5 Not greater than 0.3 Not greater than 0.2 Not greater than 0.5 Not greater than 0.2 Not greater than 2.0	 0.44 0.23 0.11 0.25 0.13 1.16
Residual Palladium by ICP	Not greater than 3ppm	2.3
Loss of Drying (% w/w)	Not greater than 0.5	<0.1
Residual solvents (ppm) Ethanol Toluene	 Not greater than 5000 Not greater than 890	 2500 600
Enantiomeric purity	Not less than 98.0%	99.1

2.2.1.P.7 Container Closure System

[18F]ABC123 Injection is collected into a sterile, presealed, pyrogen-free vial, consisting of Type 1 glass with a bromobutyl rubber stopper.

2.2.1.P.8 Stability

[18F]ABC123 Injection is prepared for immediate use.

Radiochemical stability is related to the radioactive decay. The expiration of a batch of [18F]ABC123 Injection will be determined by the initial radioactivity at the time of release for immediate administration, if the radioactivity is less than 50 MBq, it will not be used. The shelf life for the drug product will not exceed 60 minutes.