

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

2.2.1.S.1.2	Structure	
Structural For	mula	The che
Molecular For	mula	The mol
Molecular We	ight	342.6g/r
Chirality/Stereochemistry		ABC123
•		configur

The chemical structure would be provided The molecular formula would be presented. 342.6g/mol 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.
	The solubility of ABC123 sodium salt in water at
Solubility	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:

litv
- ,

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 ¹⁸O-enriched water with protons accelerated in a cyclotron according to the following reaction:

¹⁸O(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.

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 Ana	ysis of ABC123	(Batch R1234/01/1)
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Molecular Formula		
Element	% Theoretical	% Found
С	61.4	61.1
Н	5.8	5.7
Ν	7.9	7.6
CI	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 (¹H-NMR) spectrum were assigned to the protons in the molecule. The signals from a carbon nuclear magnetic resonance (¹³C-NMR) spectrum were assigned to the carbons present in the molecule. All spectra obtained were consistent with the structure of ABC123. The ¹H-NMR and ¹³C-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 3400 MHz 1 H-NMR Spectrum of ABC123 (Batch R1234/01/1) in 2% w/v DCl in D₂O

Chemical Shift	Position	# of Carbons
(ppm)		
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

13C-NMR

Figure 4 13 C-NMR Spectrum of ABC123 (Batch R1234/01/1) in 2% w/v DCl in D₂O

[The ¹H-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.

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

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

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 Street address Town Country WeMakeForU Clinical Imaging Centre The Avenue AnyTown 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/cm² of filter area (2.8 cm²) 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	109.7 min ± 5%	
Gamma energy	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	
рН	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

pН

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	WeMakeForU	WeMakeForU
		AnyTown	AnyTown	AnyTown
Test	Acceptance Criteria			
Identification	Concordant with	Conforms	Conforms	Conforms
	reference standard			
Appearance	Clear, colourless,	Conforms	Conforms	Conforms
Appearance	free from particles			
Radioactive half-life	109.7 min ± 5%	107	110	106
Gamma energy	Concordant with F-	Conforms	Conforms	Conforms
	18 energy spectrum			
Radiochemical	Not less than 00%	99 %	97 %	98 %
Purity	NOLIESS (11a11 90 /0			
	90 to 110% of 150	106%	102%	97%
	MBq/ml at the date			
Nominal activity	and time stated on			
	the label			
Content of ABC123	Not more than 1 µg	0.10	0.11	0.20
	/ml			
pН	4.5 – 8.5	6.91	7.31	6.97
	Not more than 175	14	17	8.8
Bacterial Endotoxins	EU			
	(endotoxins of gram			
	negative bacterial			
	origin)			
Sterility Testing	Complies with Ph.	Pass	Pass	Pass
	Eur.			

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		Mallana an istallin a
Description	Yellow crystalline solid	Yellow crystalline
laboration and a second second		powder
	The encetrum of the completion	Conformo
ABC 123 DY IR	concordant with that of the ABC123	Comornis
	authentic material	
ABC123 content by HPLC	Greater than 97	00.2
(% w/w)	Greater than 37	99.Z
Drug-related impurities content by		
HPLC. (% area)		
XY7123	Not greater than 0.5	0.44
XYZ456	Not greater than 0.3	0.23
PQR456	Not greater than 0.2	0.11
LM1122	Not greater than 0.5	0.25
Any unqualified impurity	Not greater than 0.2	0.13
Total		
	Not greater than 2.0	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	Not greater than 5000	2500
Toluene	Not greater than 890	
		600
		00.4
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.