SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 February 2004. For scientific information on procedures after this date please refer to module 8B.

I Introduction

DaTSCAN is a diagnostic medicinal product containing the active substance ioflupane (^{123}I) INN, (otherwise referred to as ^{123}I-FP-CIT or ^{123}I-β-CIT-FP) which is a radioiodinated cocaine analogue. This cocaine analogue is a ligand with high affinity to dopamine transporter (DaT) located on the presynaptic nerve endings (axon terminals) in the striatum. The axon terminals are projections of the dopamine neurones in the substantia nigra. Therefore, binding of DaTSCAN in the striatum is claimed to reflect the number of dopaminergic neurones in the substantia nigra. It has been developed as a dopamine transporter imaging agent for single photon emission computed tomography (SPECT). The technique is claimed to be sensitive enough to differentiate changes in the nigrostriatal dopaminergic system in patients with Parkinsonism and healthy controls.

The indication is as follows: DaTSCAN is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian Syndromes, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTSCAN is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.

Parkinson's disease is characterised by akinesia, rigidity and abnormal involuntary movements.

True Parkinsonian syndrome includes conditions like multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), in addition to Parkinson's disease. This syndrome is characterised by the loss of dopaminergic cells and the resultant decrease in striatal dopamine. The prevalence in the community of Parkinson's disease, MSA and PSP are approximately 82%, 10% and 8% respectively.

Essential tremor (ET) is often confused clinically with Parkinson's disease and related syndromes but is not associated with nigrostriatal degeneration.

DaTSCAN is presented as a sterile 5% (v/v) ethanolic solution for intravenous injection and should be used without dilution. The recommended dose for adults and the elderly is 111-185 MBq. DaTSCAN is not recommended for use in children or adolescents, as data are not available for these age groups.

Patients must undergo appropriate thyroid blocking treatment prior to injection to minimise thyroid uptake of radioactive iodine. SPECT imaging should take place between three to six hours post injection.

2. Chemical, pharmaceutical and biological aspects

Composition

DaTSCAN is presented as a sterile solution of Ioflupane (^{123}I) for intravenous injection, 2.5 ml and 5 ml in a 10 ml glass vial. The radioactivity is calibrated during manufacture to have a certain activity at a future reference time, in this case 74 MBq/ml. The product contains ethanol (5% v/v) as a solubiliser, acetic acid and sodium acetate as a buffer system and Water for Injections as a diluent. The non-radioactive analogue Ioflupane-(^{127}I) is also present.

Two presentations have been developed i.e. 2.5ml and 5ml vials, providing 185 MBq per vial and 370 MBq per vial respectively, at the reference time.

Active substance

Ioflupane (^{123}I) is a cocaine analogue with the chemical name N-ω- fluoropropyl-2β- carbomethoxy-3β-(4-iodophenyl) nortropane, or (^{123}I)-FP-CIT. It is not isolated during manufacture of the product.

It is synthesised from a key starting material Sn FP-CT via oxidative iododestannylation with sodium (^{123}I)-iodide. Specifications for sodium (^{123}I)-iodide are satisfactory (e.g. radionuclide purity not less than 99.9% on calibration and information has been provided on the generation of this raw material by irradiation of a ^{124}Xe target.

The dossier contains detailed reports on the preparation and characteristics of Sn FP-CT which determines the stereochemistry of the active substance. 150 µg aliqots of Sn FP-CT are set aside in vials for each manufacturing batch. (In mass terms the batch sizes of the active substance which carry through into the product are very small, in the submicrogram range).

Proof of structure has been shown using the 'cold' analogue (^{127}I)-ioflupane by means of the usual spectroscopic techniques and correspondence between these data and the active substance has been confirmed.

The impurities arising from the synthesis have been well described and characterised, many of them present at the submicrogram level. Impurities have been qualified with reference to toxicology studies.

Stability of the active substance has not been shown by means of conventional studies, since it is not isolated. It has been shown that aliquots of the key starting material Sn FP-CT are stable in glass vials at -20°C to -30°C, and a storage life of 24 months can be envisaged for this substance.

Other ingredients

The excipients ethanol, acetic acid, sodium acetate and water for injections are characterised according to PhEur specifications.

Product development and finished product

The formulation effectively allows the radiochemical purity of the injectable solution to be maintained throughout its storage life, and is compatible with the intravenous injection route.

During the pharmaceutical development, the following issues were especially addressed:

- The choice of active ingredient.

  This is justified as an agent for the visualisation of dopaminergic transporters. The choice was based on activity levels compatible with both the quality control appropriate to the manufacturing process, and occupation of transporter sites without producing any human pharmacological effect (1%). The choice of the radionuclide (^{123}I) was because of its very short half life.

- The problem of the ethanol content.

  Complete removal by evaporation would significantly reduce the radiochemical purity. A complete study was carried out to justify the 5% ethanol remaining. A small percentage of ethanol is useful for the solubility of the ioflupane, which is lipophilic and only moderately soluble in water.

- The pH was also thoroughly studied as a factor influencing the radiochemical purity. An acid pH of 4.7 was found most favourable.

- The choice of buffer solution concentration, and the choice of the vials and closures, are justified. European Pharmacopoeia type I glass vials, and Teflon-coated closures were chosen, these latter attenuating unwanted binding of radioactivity.

- Syringes were also studied, justifying the use of plastic syringes for administration.

Concerning the sterilisation process, measurements of radiochemical purity were made on vials of the product autoclaved at 121°C for at least 15 min. The results of these measurements proved unacceptable, a fall in radiochemical purity of 20% being recorded. Therefore, the product is manufactured by aseptic assembly, i.e. sterile filtration through a 0.2 µ filter (with relevant control of

bioburden and bubble point testing), and subsequent filling of the product into pre-sterilised containers under EU grade A environment in a grade B room.

The product test methods and specification prior to release are acceptable for a product of this type, with particular attention paid to radionuclidic purity, radiochemical identity, radiochemical purity, total activity, specific activity and sterility.

Stability of the product

Whilst the chemical stability of the active substance is not a major issue, the half-life of ^{123}I determines the short shelf-life of the product. Stability studies have been carried out at 25°C for 10 h after the stated expiry time. In addition a transport study was conducted at temperatures up to 40°C. In summary, all batches were within specifications, and the results endorse the storage conditions as defined in the SPC. Whilst the concentration of active substance is the same in both presentations, the 5 ml vial has a higher amount of radioactivity present which takes longer to decay to 'usable' levels. Therefore the 5 ml vial has a longer usable shelflife than the 2.5 ml vial.

3. Toxico-pharmacological aspects

Pharmacodynamics

Pharmacodynamics related to the proposed indication

Six *in vitro* studies and nine *in vivo* bibliographic studies are presented, carried out in the rat, mouse, monkey and baboon.

There are in addition two *in vivo* studies conducted on one analogue, and the other on several analogues of the active ingredient, respectively in the baboon and the rat.

The *in vitro* studies all demonstrated the specific binding of the active ingredient on the DaTs, in particular in the striatum.

Different substituted phenyltropanes (cocaine skeleton) had a high affinity for dopamine transporters (DaT), and high striatum/cerebellum binding ratios were found on sections of different brain tissues. Pharmacological inhibition studies confirmed binding on DaTs in the striatum.

Two studies on rat striatum and frontoparietal cortex homogenates placed in contact with these derivatives of β-carbomethoxy-3β-(4-iodophenyl)-tropane (β-CIT) confirmed this specificity and suggested that if labelled with ^{11}C, ^{18}F or ^{123}I, they could serve as PET or SPECT imaging agents. The fluoropropyl derivative (i.e. ioflupane) had the greatest selectivity and the highest affinity coefficient.

Autoradiographic comparison of the binding of three N-substituted ^{125}I-labelled ligands to the DaTs, on human brain sections, *post mortem*, confirmed the affinity for DaT-rich areas. The highest specificity was found for the fluoropropyl derivative; the active ingredient of the specialty, compared with the fluoroethyl derivative and the methyl derivative, which were the least specific. This was confirmed by the use of inhibitors of the different amines.

Besides these *in vitro* studies, *in vivo* studies are presented in the form of copies of different papers published in journals of ranging degrees of specialization.

After administration of different N-substituted analogs of β-CIT, and in particular the fluoroethyl and fluoropropyl derivatives, locomotor activity was significantly increased in the rat at doses of 0.3 to 3 mg/kg. After injection in the baboon and SPECT imaging, the striatum displayed the most binding, at all observation times between 1 h and 5 h after injection of the iodine-123 labelled compound.

In the cynomolgus monkey, a study by SPECT imaging with the ^{11}C-labelled compound showed that it accumulated in the striatum with a striatum/cerebellum binding ratio of about 8 at 60 min, steady state in the striatum being achieved in 70 to 90 min. The compound remained 80% intact in the plasma at 20-25 min. The low metabolism minimized the risk of metabolites crossing the blood-brain barrier. After injection of a high dose of β-CIT, the binding was found to be reversible. The results were confirmed by studies on human brain sections *post mortem*.

Experiments in the rat confirmed the binding specificity to the striatum versus other areas of the brain. The striatum/cerebellum ratio was close to 6 at 1 h and remained stable from 2 to 6 h after injection.

In the rhesus monkey in which the dopaminergic neurones are chemically impaired, the specific binding to the striatum was markedly reduced.

In addition, experiments in the baboon show that ioflupane had a particular sensitivity for DaTs; that for the 5HT transporters being more than three times lower.

General pharmacodynamics / safety pharmacology

Two studies, conducted in accordance with GLP, were performed one in the rat to study the behavioural effects, and the other in the dog to investigate cardiovascular effects

In the rat, the compound administered at doses of 10, 1,000 and 10,000 times the intended human clinical dose was labelled with non-radioactive iodine to be as similar as possible to the active ingredient. The modified Irwin test was used to assess the activity and the behaviour of the rats. After 7 days observation respiration was observed to be impaired (accelerated breathing or respiratory difficulties) at all three doses, and impaired muscle tone was found at only the highest dose.

In the dog, doses of 10, 100 and 1,000 times the intended human clinical dose were tested after implantation of a transmitter for telemetric monitoring of cardiovascular parameters, which were thereby measured regularly during the first hour and then every hour for 24 hours after administration.

No cardiovascular effect was observed. Respiratory effects, such as were recorded in the rat, were not observed.

A third general pharmacological report concerns possible drug interactions with the active ingredient in the rat. The drugs investigated were administered i.v. in a single dose, and subcutaneously in repeated daily doses for two weeks, except for L-DOPA for which repeated injections were not tested. The active ingredient itself was labelled with iodine-123 and the doses of psychotropic drugs were higher than those used in human therapy.

Only fluvoxamine was observed to have a negative effect on the binding of the active ingredient in the striatum, and only in the areas rich in serotonin transporters.

Dopamine agonists were not tested, because they act on postsynaptic receptors and not on transporters located presynaptically.

Pharmacokinetics

Trials were conducted in the rat, monkey and baboon with the compound labelled in different positions by one of the following radionuclides: ^{123}I, ^{11}C or ^{18}F.

The compound, although essentially and rapidly bound in the striatum, is also distributed in the liver, spleen, kidney and lung. A striatum/cerebellum ratio of 6 was found 1 h post-injection. The time course of the binding ratios prompted the choice of 2 h as time limit for the study of binding inhibition or blocking effects. The active ingredient also binds on the serotonin transporter, but less strongly than on the dopamine transporters.

The excretion route of ioflupane in the rat was sex-dependent. The females eliminated it mainly by the renal route: 56.66% in 72 h against 24.22 in feces. For males these percentages were respectively 36.03% and 45.71%.

In the baboon (females only), it was found that the thyroid, even when not blocked by prior administration of iodine, retained no radioactivity, implying no release of free iodine in the body from the active ingredient, which is 90% bound to serum proteins.

The doses absorbed by the different organs were calculated by the MIRD method. The lower colon is the main target organ, followed by the liver, the upper colon, the bladder wall, the thyroid, the kidneys, etc. The doses delivered to these organs are about 0.2 mGy/MBq and the equivalent of the effective dose is 0.08 mSv/MBq.

The biodistribution of the radioactivity after injection of ioflupane (^{123}I) was also studied in the male rat. The organs that retained most radioactivity were the liver (up to 24 h post-injection), the lung (up to 3 h), and the striatum, which dislayed the highest labelling from the first hour post-injection.

The metabolism studies in the monkey and healthy human volunteers allowed a comparison between cocaine, β-CIT and the active ingredient. The metabolites were different according to the site of labelling with ^{18}F, ^{11}C or ^{123}I.

In both humans and monkeys, the main metabolite of the active ingredient is FP-CIT acid, a polar compound unable to cross the blood-brain barrier. It is eliminated as glycuronyl conjugates. The other metabolites can be nor-β-CIT, traces of which have been detected, and free iodine, which was not detected. Although free iodine was not detected, it is advisable to block the thyroid by preventive administration of iodide before injection of DaTSCAN, and this is reflected in the SPC.

Toxicology

Single dose toxicity

In the rat, 2 dose levels were administered: the high dose was chosen because it was the LD50 for cocaine and the low dose represented 10,000 times the intended human dose.

. at high dose : 17.5 mg/kg, i.v.:

5/5 males and 3/5 females died within 24 h: clinical signs observed included lethargy, clonic spasms, ventro-lateral recumbency, hunched posture, increased activity, uncoordinated movements, laboured respiration, piloerection, shaking of the head.
In the two surviving females the symptoms disappeared in 24 - 48 h.

. at low dose : 0.06 mg/kg, i.v.:

there was no mortality or signs of systemic toxicity, although intense movements of discomfort were observed during injection. Body weight gain was normal in all surviving animals.

In the rabbit, only one dose level of 0.06 mg/kg in the marginal ear vein was used.

During the treatment intense reactions consisting of shaking and withdrawal of the head and high tensions in the paws and body were observed in 3/5 animals.

For the remaining animals the test solution was warmed to 30° C; thereafter less severe reactions occurred. It seemed that temperature and low pH were responsible for this behaviour reaction. In later studies the volume of injection was greatly reduced, from 2 to 0.5 ml/kg.

Reactions at the injection site in some animals were attributed to the mechanical procedure or to the vehicle. In the absence of a control group no conclusion can be drawn.

No animals died during the study and macroscopic post mortem examinations on day 15 did not reveal any abnormalities.

Repeated dose toxicity

In the rat, after a preliminary dose range finding study, 3 dose levels were selected and administered under a dosage volume of 2.5 ml to 10 animals/sex/group: 0-0.006-0.6 and 3.6 mg/kg.

At the high dose (3.6 mg/kg) stereotype behaviour, hyperactivity, hypersensitivity to external stimuli, and piloerection were observed in both sexes.

At the intermediate dose (0.6 mg/kg) similar signs but with less severe intensity were seen only in the female group.

Body weight gain was decreased only in the high dose group.

Biological changes were noted for serum protein and albumin (3.6 mg/kg) and bilirubin (0.6 and 3.6 mg/kg), which were significantly reduced.

At necropsy some organ weights were increased in both sexes (brain) and in females (kidney, ovaries, thymus) in the high dose group.

Microscopic examination did not reveal any changes except at the injection site in all groups including controls: this tissue damage consisted of perivenous inflammation; fibrosis, haemorrhage, thrombosis, necrosis of veins and oedema.

In the rabbit, based on a preliminary dose ranging study, dose levels selected for the main study were: 0.006 - 0.6 and 1.5 mg/kg were administered i.v. to 4 groups of 4 animals/sex for 14 days.

In the high dose group 2 animals died, one male and one female. Clinical signs include stereotypic and aggressive behaviour, exaggerated response to external stimuli, exophthalmia with dilated pupils, fast and laboured respiration.

In the other groups (0.6 and 0.006 mg/kg) similar but very moderate signs were observed.

Vocalisation and violent reactions occurred in all groups including controls, during treatment.

Weight gain and food consumption were lower in the high dose group than in controls.

Increases in serum urea, CK and LDH values in all groups including controls were attributed to tissue damage at injection site.

A decrease in serum bilirubin was observed in both sexes, statistically significant in females of intermediate and high groups.

At necropsy no abnormality in organs were observed with the exception of injection site lesions in all groups including controls. These lesions were like those in the rat, characterised by perivenous haemorrhage, oedema, inflammation, fibrosis, thrombus formation and endothelial necrosis.

In summary, the salient findings were of behavioural type and attributed to the pharmacological effects of this cocaine-like product.

Reproductive Toxicity

No studies have been conducted.

The SPC contraindicates the use of DaTSCAN in pregnancy.

In the CPMP's opinion, since no gene mutations or chromosomal changes have been evidenced, and as well as no effects on reproductive organs in toxicity studies on 2 species after 14 daily intravenous administrations of up to 100,000 fold the clinical dose, the absence of a fertility study in rodents can be accepted, given that a very low single dose will be used (0.006 micro g/kg) in humans.

Genotoxicity

Mutagenicity

As in toxicity studies the genotoxic potential of DaTSCAN was investigated with a non-radioactive product.

In the Ames test a small and not dose-dependent increases in revertants in TA 100 and TA 98 was observed in one independent experiment, which can be considered to be incidental.

There was no sign of genotoxicity in the mouse micronucleus test.

Overall there was no evidence of genotoxicity under the experimental conditions employed.

Carcinogenicity

Carcinogenicity studies have not been conducted, which is acceptable for a product intended for single administration. This is mentioned in the SPC.

Local tolerance

A single dose study was conducted in the rabbit and the rat to assess the tolerance potential of FP-CIT by intravenous, intraarterial or perivenous route.

All animals exhibited tachypnea after treatment and vocalised during injection.

After 5 days observation injection site areas were examined macro and microscopically:

erythema and oedema were seen at all injection sites in all groups, although the control ears were less injured than the treated ears.

Microscopic examination revealed periarterial fibrosis, oedema and haemorrhages with the same severity in controls and treated samples.

In the tolerability studies with the vehicle the results indicated that the rabbit was more sensitive to injection that the rat.

A blush discoloration and slight oedema was observed in all rabbits, whereas no local effect appeared in the rats.

This poor tolerability in the rabbit may be partly attributed to the vehicle for probably 2 reasons: the low pH and the large injection volume. However, the product was well tolerated locally in rats.

Ecotoxicity/environmental risk assessment

No significant environmental risk is anticipated by the use of DaTSCAN in accordance with the SPC

4. Clinical aspects

The clinical development program carried out by the company consists of two main efficacy studies (open) in support of the claimed indication: **CY96.FP.II & DP 008-003.** A total of 254 patients were evaluated in these studies. In addition, 4 published studies were presented as supportive evidence of diagnostic efficacy.

The safety database consists of 454 patients exposed to DaTSCAN : (266 in the main studies above, 88 in the supportive studies and 100 in ongoing studies).

Clinical pharmacology

Pharmacodynamics

In patients with Parkinson's disease, a marked reduction in dopaminergic neurones in the striatum has been observed. The axon terminals are projections of the dopamine neurones in the substantia nigra. The action of dopamine at the synapse is terminated by rapid reuptake into dopaminergic nerve endings. This is achieved by the dopamine transporter (DaT) which is neurotransmitter-specific, high affinity, sodium-dependent transmembrane transporter protein. This can be blocked by psycho-stimulant drugs (e.g. cocaine), neurotoxins (e.g.1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and various specific pharmacological markers.

Ioflupane (^{123}I)'s affinity for the dopamine transporter has been shown in pre-clinical studies.

High affinity for the dopamine transporter has been demonstrated by benzoyltropane cocaine. This is inactivated rapidly and metabolically by hydrolysis of the 3β-benzoyl ester. Cocaine analogues have been developed which avoid hydrolysis of the ester by attaching the aromatic ring directly to the tropane system.

In a published study, both ioflupane (^{123}I) and (^{123}I)β-CIT showed decreased striatal uptake in Parkinson's disease patients compared to controls.

Another study showed the order of specificity to be β-CIT-FP (ioflupane) > β-CIT-FE > β-CIT by autoradiography in postmortem human brains. In another study in postmortem human brains, there was a high binding in the caudate and putamen and low binding in the cortex and other regions.

Safety and tolerance of ioflupane (^{123}I) has been demonstrated in phase II studies.

Secondary pharmacology has not been investigated but in pivotal studies, no effects were observed on pulse and blood pressure.

As the maximum degree of dopamine transporter occupancy in humans was <1%, no pharmacological effect was expected.

The evidence for primary pharmacology has been mainly derived from pre-clinical studies. The rationale for development of the tracer has been provided.

Pharmacokinetics

Limited kinetic studies were performed. In view of the I.V. injection, 100% availability can be assumed. The physical half life of ^{123}I is 13.2 hours.

Biodistribution, safety and tolerability**:** In a phase I biodistribution and dosimetry study in 12 healthy volunteers, whole body scans were performed up to 48 hours following injection of 100 MBq ioflupane (^{123}I).

The level of radioactivity were highest in the lungs, liver and brain. The images showed rapid lung uptake and hepatobiliary excretion. The highest absorbed doses were in the urinary bladder wall and lungs. Brain uptake was approximately 7% of the % injected activity, with 30% of this concentrated in the striatum. The mean urinary excretion was 60% ± 9% and mean predicted faecal excretion was 14% ± 1%.

Radiation dose estimates confirmed an effective dose of 0.024 mSv/MBq.

The tolerance was good and no adverse events were reported.

Comparison of (^{123}I)β-CIT and ioflupane (^{123}I) for imaging of the dopamine transporter :

In a pilot study, both tracers produced excellent images and effective dose equivalent of both tracers were similar. The faster striatal washout of FP-CIT resulted in 40% reduction in estimated radiation dose to the basal ganglia, compared to that for β-CIT.

Human biodistribution and dosimetry of ^{123}I-fluoroalkyl analogues of (^{123}I)β-CIT.: In a study in six healthy volunteers, the peak percent injected dose uptake were:-

	FE-CIT	**FP-CIT**
Liver	28% ± 7%	25% ± 6%
Lungs	13% ± 5%	19% ± 6%
Brain	8% ± 2%	7% ± 2%
Spleen	6% ± 2%	8% ± 2%
Bladder	5% ± 1%	4% ± 1%

Both showed similar pattern of distribution. Radiation dose estimates were lower for FP-CIT.

Metabolism: Only one metabolite has been identified in human plasma, which was believed to be free carboxylic acid formed by enzymatic hydrolysis of the methyl ester group.

Drug interactions: Drugs with high affinity for dopamine transporter may have an effect on the clinical efficacy of ioflupane (^{123}I). Compounds likely to interact with striatal uptake through dopamine transporter should not be used (cocaine, amphetamine, mazindol, methylphenidate and benztropine).

There was pre-clinical evidence that drugs like levodopa, selegiline, haloperidol, risperidone and fluvoxamine were unlikely to affect the uptake of ioflupane (^{123}I) by the dopamine transporter.

As dopamine agonists (bromocriptine, pergolide and ropinirole) target the post-synaptic dopamine receptor, they were not expected to interfere with pre-synaptic dopamine transporter imaging.

In general, kinetic studies were limited but acceptable for the proposed indication, i.e. single administration. Absorption can be assumed to be 100% and excretion profile has been adequately described. There were no studies in special risk groups and none was considered essential, however, an appropriate statement has been included in the SPC under Section 4.4. Information relating to drug interaction is reflected in the SPC, Section 4.5.

Dosimetry: Effective Dose, calculated according to the 'MIRD DOSE 3.1' method, is 0.024 ± 0.002 mSv/MBq. The urinary bladder wall represents the critical organ (0.054 ± 0.008 mGy/MBq) but lungs (0.043 ± 0.002 mGy/MBq) and lower large intestine wall (0.042 mGy/MBq) are also the most concerned by radiation absorption doses. The self dose to striatum is estimated at 0.23 ± 0.07 mGy/MBq). These data do not give rise to concern.

- For a 70 kg individual, the effective dose (ED) resulting from injection of DaTSCAN, is 4.35 mSv which is acceptable. As an indicative comparison, the ED of a cerebral perfusion SPECT is 4.5 to 5 mSv, the ED of a bone scan is 5.6 mSv.
- The SPC includes relevant advice for accelerating intestinal clearance in case of overdosage.

Clinical efficacy:

Dose-response studies and main clinical studies

Two main studies were submitted, both sponsored by the applicant:

Study	Methodology	Number/ Population	primary efficacy parameter	secondary efficacy parameter(s)
CY96. FP.II	Open, single centre, controlled, non randomised, parallel group, SPECT / methodology unspecified ROIs tracing methodology unspecified	10 healthy volunteers (mean age = 53) 20 clinically diagnosed idiopathic PD patients (mean age = 57)	**Time of uptake of ioflupane (^{123}I)	Ratio of specific to non specific uptake up to 6 hours. i.e. Ratio = (striatum uptake minus occipital cortex***uptake) / occipital cortex uptake)
DP 008-003	Open, uncontrolled*, multicentre, non randomized, parallel group SPECT / methodology unspecified comparison of PS versus ET patients	160 PS patients related to PD, MSA, PSP (mean age =62.8) 29 Essential Tremor patients (mean age=64.1) 35 healthy volunteers* mean age =61.1)	Unblinded visual assessment of images at study centre (qualitative assessment)	-Blinded read , panel of 5 readers. (qualitative assessment) -Semi-quantitative assessment of regions of interest (Ratio of specific to non specific uptake)

* These volunteers were used in each centre to calibrate the SPECT and in semi quantitative analysis but not as controls.
** Not actually defined as a primary efficacy parameter in the protocol.
*** Occipital cortex is considered as a 'non specific' binding region.

Study CY96.FP.II: In this Phase II, single centre, open study, uptake kinetics of ioflupane (^{123}I) in various brain regions was investigated. A comparison was made between patients with Parkinson's disease and healthy volunteers. A total of 30 subjects (20 patients and 10 healthy volunteers) received single injection of approximately 111MBq ioflupane (^{123}I).

Imaging between 3 - 6 hours showed ratio of specific to non-specific striatal uptake to be significantly different between Parkinson's disease group and healthy volunteers. Ipsilateral changes, i.e. clinically asymptomatic side, were seen in a subgroup analysis suggesting that the product has potential for early diagnosis of Parkinson's disease.

Study DP008-003: This was a multicentre, open, non-controlled and non-randomised Phase III trial. The study compared the striatal uptake of ioflupane (^{123}I) in patients diagnosed with true Parkinsonian syndrome (Parkinson's disease, multiple system atrophy and progressive supranuclear palsy) and definite essential tremor. The study period was six months.

A total of 250 subjects were recruited (212 patients and 38 healthy volunteers) and 224 analysed (189 patients and 35 healthy volunteers).

Objectives/efficacy variables

The primary efficacy criteria were visual assessment of ioflupane (^{123}I) striatal uptake determined by institutional read (clinical diagnosis of the patient by the study site). The secondary variable was visual assessment of striatal uptake determined by blinded read (consensus diagnosis of a panel composed of 5 readers, blinded to the clinical diagnosis). In addition, a semi-quantitative assessment of regional interest was also determined.

In general, the objective was to compare the accuracy of diagnosis by DaTSCAN to the best possible clinical diagnosis, according to movement disorder specialists.

Results

In this study a high degree of sensitivity and specificity was reported with reference to the clinical diagnosis, both for institutional read and blinded read, as shown in the summary table below:-

Considering that the true gold standard in this case is post-mortem examination, clinical diagnosis according to movement disorder specialists was taken as the reference.

'Sensitivity'	Unblinded read (primary) % Lower bound of the 95 % Confidence Limits (LCL)	Blinded read(secondary) % Lower bound of the 95% Confidence Limits
per protocol analysis	111/115 = 96.5% LCL = 91.9%	109/115 = 94.8% LCL = 89.7%
ITT analysis	154/158 = 97.5 % LCL = 94.1 %	150/158 = 94.9 % LCL = 90.8%

'Specificity'	Unblinded read (primary) % Lower bound of the Confidence Limits (LCL)	Blinded read(secondary) % Lower bound of the Confidence Limits
per protocol analysis	16/16 = 100 % LCL = 80.6%	15/16 = 93.8% LCL = 72.2%
ITT analysis	27/27 = 100 % LCL = 87.8%	25/27 = 92.6 % LCL = 77.5%

The patients included in this trial were mostly established cases of true Parkinsonian syndrome, and these are probably not the whole patient population where the product is to be used.

However, the striatal uptake of ioflupane (^{123}I) was clearly decreased in patients with Parkinson's disease and related syndromes, (some patients with multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) were also included). Although this diagnostic procedure can differentiate between ET (essential tremor) and true PS (Parkinson's disease and related syndromes), there is no evidence that it can differentiate between PD, MSA or PSP and this is reflected in the SPC section 4.1, indication.

10 'mismatch' cases were observed (approx. 5% of the study population), i.e. the SPECT image did not correlate with clinical diagnosis. This led to a re-diagnosis in 5 cases e.g. from PD to essential tremor, non-parkinsonism, vascular disease, neuroleptic-induced parkinsonism and from MSA (multiple system atrophy) to essential tremor. The other cases are under ongoing monitoring and followup. This indicates that the symptomatology may not be as reliable a predictor of the underlying pathology as imaging by DaTSCAN.

Clinical studies in special populations

No specific populations have been studied other than those reported in the main studies.

Supportive studies

The following published studies were submitted as supportive of diagnostic efficacy. All used the formulation intended for marketing and were published in peer-reviewed journals.

Practical benefit of ioflupane (^{123}I) SPECT in the demonstration of dopaminergic deficit in Parkinson's Disease: This was a small study in five patients. SPECT images were acquired at 3 hours post-injection for ioflupane (^{123}I) and 24 hours post-injection for (^{123}I) β-CIT. Both tracers were good markers for imaging of the DA transporter in PD patients, however ratios of specific to non-specific striatal ioflupane (^{123}I) uptake were 2.5 fold lower than those observed following injection of (^{123}I) β-CIT. The mean uptake was more decreased in the putamen than in the caudate nucleus with both tracers.

Striatal dopamine transporter labelling in early and advanced Parkinson's Disease: This study evaluated the use of ioflupane (^{123}I) in early and late stage Parkinson's disease. Eighteen patients with Parkinson's disease (6 early and 12 late stage) and six healthy volunteers were recruited.

There were significant differences in uptake, between control and early Parkinson's group, control and late Parkinson's group and between early and late Parkinson's patients.

This study gave clear indication of decreased uptake of ioflupane (^{123}I) in patients with early Parkinson's disease.

ioflupane (^{123}I) SPECT in healthy volunteers and early stage, drug naïve Parkinson's disease: In this study, the ratio of specific to non-specific striatal binding was investigated in 21 drug naïve Parkinson's disease patients and 14 healthy volunteers.

All striatal ratios were lower in patients with Parkinson's disease, compared to controls. This difference was significant. The reduction was more marked in the putamen.

Imaging of dopamine transporters with ioflupane (^{123}I) in healthy controls and patients with Parkinson's disease (test/retest variability)..

In 10 patients with Parkinson's disease and 6 healthy volunteers, reliability and reproducibility of the technique were investigated.

No significant differences were noted in test/retest studies. The results in PD patients are shown below:

Variability and reliability between test and retest in 10 patients with Parkinson's Disease

		ROI protocol			3.1 VOI protocol		
Subject	**Age(yr)**	**Test***	**Retest***	**Variability****	**Test***	**Retest***	**Variability****
1	76	2.02	2.07	2.51	2.34	2.30	2.07
2	71	1.43	1.35	5.45	1.37	1.31	4.62
3	68	1.60	1.56	3.06	1.57	1.43	9.51
4	57	1.77	1.90	7.13	1.77	1.91	7.81
5	68	2.21	2.09	5.69	2.20	2.27	3.40
6	65	1.88	1.95	3.52	2.07	2.17	4.47
7	71	1.66	1.57	5.35	1.68	1.72	2.19
8	57	1.79	1.62	9.94	2.03	1.84	10.03
9	63	1.56	2.02	26.00	1.61	2.02	22.95
10	77	1.94	1.75	10.34	1.64	1.54	6.52
Mean ± s.d.		1.78 ± 0.23	1.79 ± 0.25	7.90 ± 6.89	1.83 ± 0.31	1.85 ± 0.35	7.36 ± 6.16
Reliability***			1.00			0.96	

* Data expressed as ratio of striatal to non specific binding
**Absolute values of the test/retest difference expressed as percentage of the mean of the test and retest measures.
***Intraclass correlation coefficient (p).
ROI = region of interest: VOI = volume of interest.

This small study showed the reliability of the technique.

SPECT imaging of striatal dopamine transporters and D2 receptors in patients with autosomal recessive doparesponsive dystonia: The deficiency of tyrosine hydroxylase (TH) has been reported in a recessive form of dopa-responsive dystonia (DRD). The ratio of specific to non-specific striatal ioflupane (^{123}I) binding were high in comparison with those reported for healthy adult volunteers. This indicated that extrapyramidal symptoms in this condition were unlikely to be due to degeneration of the dopaminergic nigrostriatal pathway.

(This study was not directly relevant to the indications sought by the company).

The supportive studies confirmed decreased striatal uptake of Iodine-123-ioflupane in patients with Parkinson's disease and reliability of the technique in a one-day procedure.

Clinical safety

Patient exposure

454 subjects as a total were exposed to DaTSCAN: 266 enrolled in the main studies (57 healthy volunteers and 209 patients, mainly PD patients), 88 from supportive studies and 100 from on going studies.

The activity used in the applicant-sponsored (main) studies ranged from 88 to 200 MBq.

Adverse events and serious adverse events/deaths

Although a global safety summary has not been provided, the company expert's comments did include an overall view of the safety of the product.

No deaths were reported.

There were two severe adverse events (headache and extrapyramidal syndrome - one case each). Both occurred in patients with true Parkinsonian syndrome. A total of 65 adverse events were reported out of which 30 were probably or possibly related to the product. Most of these events were headache, vertigo and increased appetite.

There were no adverse events in Phase I and II studies. No significant changes were noted in vital signs, ECG and clinical laboratory parameters.

Safety in main study CY96.FP II: Only one out of 30 subject in this study reported an adverse event - exacerbation of a PD symptom at approximately two hours post injection (severe `off phase'). No other adverse events were recorded during this study.

Safety in main study DP 008 - 003: Out of 224 patients/healthy volunteers in this study, 65 adverse events were reported in 36 subjects. Thirty events (46.2%) were probably related to the injection. All adverse events reported in this study are shown in the table below:

Summary of all adverse events

Adverse Event	**HV** (n = 35)	**ET** (n=29)	**PS** (n=160)
Asthenia	0(0.0%)	1 (3.4%)	0 (0.0%)
Chest Pain	0 (0.0%)	1 (3.4%)	0 (0.0%)
'Flu' Syndrome	2 (5.7%)	1 (3.4%)	3 (1.9%)
Headache	2 (5.7%)	1 (3.4%)	11 (6.9%)
Injection Site Haemorrhage	1 (2.9%)	2 (6.9%)	2 (1.3%)
Injection Site Reaction	0 (0.0%)	0 (0.0%)	1 (0.6%)
Lab Test Abnormal (CPK)	0 (0.0%)	0 (0.0%)	1 (0.6%)
Malaise	1 (2.9%)	0 (0.0%)	1 (0.6%)
Pain	0 (0.0%)	0 (0.0%)	2 (1.3%)
Constipation	0 (0.0%)	0 (0.0%)	1 (0.6%)
Dry Mouth	1 (2.9%)	1 (3.4%)	0 (0.0%)
Increased Appetite	1 (2.9%)	1 (3.4%)	1 (0.6%)
Nausea	1 (2.9%)	1 (3.4%)	1 (0.6%)
Thyroid Disorder	0 (0.0%)	0 (0.0%)	1 (0.6%)
Anaemia	0 (0.0%)	0 (0.0%)	1 (0.6%)
Hypoproteinemia	0 (0.0%)	0 (0.0%)	1 (0.6%)
Bursitis	0 (0.0%)	0 (0.0%)	1 (0.6%)
Extrapyramidal Syndrome	0 (0.0%)	0 (0.0%)	1 (0.6%)
Hypertonia	0 (0.0%)	0 (0.0%)	1 (0.6%)
Parasthesia (formication)	0 (0.0%)	1 (3.4%)	1 (1.3%)
Tremor	0 (0.0%)	0 (0.0%)	1 (1.3%)
Vertigo	0 (0.0%)	0 (0.0%)	4 (2.5%)
Cough Increased	0 (0.0%)	1 (3.4%)	0 (0.0%)
Dyspnea	0 (0.0%)	0 (0.0%)	1 (0.6%)
Albuminuria	0 (0.0%)	0 (0.0%)	1 (0.6%)
Hematuria	0 (0.0%)	0 (0.0%)	1 (0.6%)
Kidney pain	0 (0.0%)	1 (3.4%)	0 (0.0%)
Urinary Tract Infection	0 (0.0%)	0 (0.0%)	1 (0.6%)

Multiple occurrences of the same adverse event within a patient/volunteer were collapsed to the adverse event of maximum (worst) severity.

Laboratory findings

Laboratory data were analysed in the pivotal studies.

No significant abnormalities were observed in haematological and blood chemistry evaluations in the phase II study.

Study DP 008-003 which had larger number of patients showed some abnormalities in platelet count, prothrombin time, creatinine, ASAT, ALAT, Gamma-GT, LDH, CPK, CK-MB and CK-MM.

Platelet count The mean value of platelet count was marginally higher in patients with PS compared to patients with ET (essential tremors) and HV (healthy volunteers). The minimum values in these patients were lower and maximum values higher, compared to HV and ET group.

Prothrombin time The maximum values of prothrombin time were significantly higher in PS patients, compared with HV and ET patients.

Serum creatinine Although the mean values were similar in all three groups, the minimum and maximum values in patients with PS were lower and higher respectively, even at screening.

ASAT: The maximum values were higher in PS patients even at screening.

ALAT: Although there were no differences in mean values in three groups, the minimum values were lower and maximum values higher in PS patients.

Gamma-GT: The mean values were similar in all the groups but the maximum values were higher in patients with PS, even at screening.

LDH: In PS patients, the minimum values were lower and maximum values were higher compared to HV and ET patients.

CPK: Higher values were noted in patients with PS even at screening. This was true for CK-MB also. The mean CK-MM values were higher at imaging in patients with PS. The minimum values were lower and maximum values higher than other groups.

Safety in special populations

No specific populations have been studied other than those patients reported in the main studies.

5. Overall conclusions and benefit/risk assessment

Quality

The applicant has developed a product of satisfactory quality in relation to the clinical use, i.e. a stable, sterile solution suitable for injection. The manufacturing process has been validated and provides a satisfactory assurance that the product will be sterile when opened for the first time. Methods used for batch control and stability studies have been validated and should ensure a product of reproducible quality.

Pre-clinical safety

The preclinical dossier is satisfactory on the whole in that it demonstrates that the active ingredient of the product presented has the pharmacological properties and the kinetics suitable for the intended application.

The doses tested were well chosen and leave a wide safety margin for any unexpected side effects, not likely anyway given the low chemical dose administered (6 ng/kg). The vehicle was in most cases that intended for the product for marketing.

The general pharmacology trials concerned only the cardiovascular domain, and general behaviour. However, the toxicity studies do not suggest any likelihood of adverse effects on digestive or other domains, given the low dose administered (6 ng/kg).

Clinical safety

From the data submitted, DaTSCAN may be considered as safe and well tolerated.

Overall there were no concerns relating to laboratory abnormalities.

Clinical efficacy

DaTSCAN is able to detect loss of functional dopaminergic neuron terminals in the striatum by means of visual assessment of SPECT images.

Therefore it may have a role in helping specialists to differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. There was no experience with types of tremor other than Essential Tremor. On the evidence available, it is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.

The specificity and sensitivity were high with reference to clinical diagnosis in the absence of a practical gold standard, i.e. post-mortem examination.

Benefit/risk assessment

During the evaluation of this product, there were concerns over its clinical usefulness, i.e. is the differential diagnosis of Parkinsonian Syndromes related to PD, PSP or MSA versus ET useful for the patient or the health care provider? Furthermore there were methodological concerns related to the fact that the patients in the Phase III studies were mostly established cases of Parkinsonism, and these are probably not the patient population where the product is to be used. It was initially not clear whether ongoing studies could be modified to provide relevant and useful information.

These concerns were summarised in the following list, and in order to assist the CPMP to come to an opinion, this list of issues was given to an ad hoc group of experts to consider. -

1. Is there a rôle for a diagnostic product such as DaTSCAN in the early differential diagnosis by specialists of Parkinsonism versus Essential Tremor?
2. What would be the benefit to the patient and his/her management arising from the use of this product?
3. Could the patient population which would benefit from this agent be defined, and are the data sufficient to support it?
4. The sensitivity and specificity of the test have been derived from a population in which the diagnosis of Parkinsonism was clinically very probable, i.e. derived from a population in which the diagnosis was established and in a later stage. The test will be used in patients in whom the diagnosis is difficult and uncertain. The group should consider the relevance of extrapolating sensitivity and specificity from one patient population to the other.
5. Are the criteria for differentiating normal & abnormal scans sufficiently well described to establish a reliable 'cutoff' between positive and negative tests, thus enabling a valid estimation of the proportion of false positives and false negatives?
6. The applicant will supply separate details on currently ongoing studies. If there are doubts concerning the answers to questions 3, 4 and 5, is it likely that the results of the ongoing studies would be relevant and helpful in order to clarify the answer?
7. If the response to question 6 is "no", does the group believe that it is feasible to undertake a further study to support the proposed indication and obtain useful results within, say, 15 months?

Following the report of the ad hoc group and further discussion by CPMP, the CPMP reached the following conclusions -

- There is a role for a diagnostic product such as DaTSCAN in the differential diagnosis by movement disorder specialists. From the evidence available it is a good indicator of functional striatal dopaminergic neuronal loss.
- It was agreed that patients would benefit from the greater diagnostic confidence afforded by the use of DaTSCAN. This would avoid inappropriate therapy and enable better patient information/advice to be given. The degree of benefit depends on the predictability and reliability of imaging with DaTSCAN, which appears to be good.
- It was considered by the experts in nuclear medicine and movement disorders that the data are sufficient to discriminate between patients with defective and intact nigrostriatal pathways. The patient population which would benefit from DaTSCAN and which was supported by the data in the dossier was described by the indication.
- In addition, it was agreed that there should be a statement in section 5.1 of the SPC to the effect that there was no experience in patients with types of tremor other than essential tremor.
- The methodological issue was the most difficult to decide, i.e. the validity of extrapolation from the Phase III clinical trial population to the early stage patient population for which DaTSCAN would be indicated. The limitations of the Phase III study were discussed, in particular, the open design and the short duration of follow-up. However , the CPMP were reassured with regard to the following points :
- in all of the patients with Hoehn &Yahr stage 1 Parkinson's disease (unilateral symptoms only) the DaTSCAN images were abnormal bilaterally.
- in these images striatal uptake was decreased on average by 50% on the contralateral side and 30 - 35% on the ipsilateral side.
- it is accepted amongst experts in movement disorders that by the time that patients with Parkinson's disease become symptomatic they have already lost 30 – 50% of nigrostriatal dopaminergic neurones. Thus any symptomatic patient, however early, would be expected to have an abnormal DaTSCAN image.
- Preliminary information was available from an ongoing study regarding imaging with DaTSCAN in patients with early Parkinson's disease
- In a study in patients with clinical diagnosis of Lewy bodies dementia, DaTSCAN diagnosis agreed with neuropathology in 5 post-mortem examinations. The clinical diagnosis was consistent with post-mortem findings in only one of these five cases.
- Discussion of the above information persuaded the majority of CPMP Members that it was possible in this case to extrapolate from one patient population to the other. Those not persuaded felt that although the proof of concept was convincing, absolute confirmation was not yet available.
- With respect to false negative scans, because significant neuronal loss occurs before the appearance of symptoms in a patient with Parkinson's disease, it was felt that a clear cut off between normal and abnormal scans should always be discernible. With respect to false positive and false negative scans, CPMP were reassured by the high degree of concordance between the blinded read and the institutional read in the Phase III study.
- It was agreed that ongoing studies could provide useful information. It was felt that one study in particular (PDT 03004) could be made more useful by protocol amendments to increase the sample size, to increase the duration of follow up, and to ensure independent (and blinded) clinical follow up. (This study includes patients with early features of parkinsonism compared with healthy volunteers). The CPMP requested the applicant to provide the results of this study as a post-authorisation follow-up measure - details are set out in Section II.3 of this report. (The long time allowed for submission of these results may be justified by the nature of the disease and its progression).

Concerning safety, the risk is considered to be low; DaTSCAN appears to be safe and well-tolerated.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority decision that the benefit/risk profile of DaTSCAN was favourable in the following indication:

DaTSCAN is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian Syndromes, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTSCAN is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.