Whole-body biodistribution and radiation dosimetry of the cannabinoid type 2 receptor ligand [11 C]-NE40 in healthy subjects

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Abstract

Purpose: The type 2 cannabinoid receptor (CB2R) is part of the human endocannabinoid system and is involved in central and peripheral inflammatory processes. *In vivo* imaging of the CB2R would allow study of several (neuro)inflammatory disorders. In this study we have investigated the safety and tolerability of [^{11}C]-NE40, a CB2R PET ligand, in healthy human male subjects, and determined its biodistribution and radiation dosimetry.

Procedure: Six healthy male subjects (age 20-65 years) underwent a dynamic series of 9 whole-body PET/CT scans for up to 140 minutes, after injection of an average bolus 286 MBq of [^{11}C]-NE40. Organ absorbed and total effective doses were calculated through OLINDA.

Results: [^{11}C]-NE40 showed high initial uptake in the spleen and a predominant hepatobiliary excretion. In the brain, rapid uptake and swift washout was seen. Organ absorbed doses were largest for small intestine and liver, with 15.6 and 11.5 µGy/MBq, respectively. The mean effective dose was 3.64 ± 0.81 µSv/MBq. There were no changes with ageing observed. No adverse events were encountered.

Conclusions: This first-in-man study of [^{11}C]-NE40 showed an expected biodistribution compatible with lymphoid tissue uptake and appropriate fast brain kinetics in the healthy human brain, underscoring the potential of this tracer for further application in central and peripheral inflammation imaging. The ED is within the typical expected range for ^{11}C ligands.

Key words: biodistribution, dosimetry, positron emission tomography, [^{11}C]-NE40, CB2R

Introduction

The type 2 cannabinoid receptor (CB2R), isolated and structurally characterized in the early nineties of the past century [1], is part of the endocannabinoid system (ECS), together with the type 1 (CB1R) receptor. Both the cannabinoid type 1 (CB1R) and CB2R are G-protein coupled receptors (GPCR's), that are quite divergent in structure with only 44% overall homology [2]. In contrast to the CB1R, which is the most abundant GPCR in the central nervous system (CNS), the CB2R is widely expressed in immune-related tissues and organs, with high expression levels in spleen, tonsils and leucocytes [3]. Outside the immune system, CB2R is expressed to a lesser extent in salivary gland, skeletal muscle, pancreas, ovary and testis [4-8]. In non-pathological conditions, cerebral CB2R expression is very low and only present in the cerebellum and pons [9-10]. CB2Rs are upregulated in inflammatory conditions by activated microglia, are involved in the production of nitric oxide (NO) and cytokines [11]. Furthermore, the CB2R is involved in pain processing [12].

There is accumulating evidence that the ECS is involved in the pathogenesis and clinical expression of neurodegenerative disorders, in part through the process of neuroinflammation [13-14]. Upregulation of CB2R has been described postmortem in patients with Alzheimer's disease (AD) [15] , Huntington's disease (HD) [16] and Parkinson's disease (PD) [17]. Therefore, positron emission tomography (PET) imaging of CB2R in the CNS can provide a tool to investigate the in vivo importance of CB2R in central inflammatory disorders.

Whereas several PET radioligands have been validated for the CB1R [18-20], only more recently attempts to radiolabel probes for CB2R have been undertaken [21]. A carbon-11-labeled CB2-selective PET tracer was described but without penetration of the blood-brain-barrier (BBB) [22-23], limiting its applicability to peripheral visualization of the CB2R. Recently, we have developed and validated novel specific radioligand for CB2R PET, 2-oxo-

7-[^{11}C]-methoxy-8butyloxy-1,2-dihydroquinoline-3-carboxylic acid cyclohexylamide ([^{11}C]-NE40). This PET ligand is fairly lipophilic (distribution coefficient (logD) of 3.9 and total polar surface area (tPSA) of 80.42 Å²) [24]. In vitro ligand binding studies using Chinese hamster ovary (CHO) –cells expressing the human CB2R have shown that NE40 has a relatively high binding affinity (Ki = 9.6 nM), which was confirmed by in vivo CB2R binding in mouse spleen [22, 24], and high specificity (100-fold over the CB1R). Radioligand safety was investigated by toxicity studies including genotoxicity (Ames test) and histopathologic evaluation in rats [25] under the microdosing concept [26]. In vivo binding in a rat model with adeno-associated viral human CB2R overexpression was confirmed [27]. Here we describe the first-in-man imaging studies, with safety and dosimetry assessment in both young and elderly male volunteers.

Materials and methods

Subjects

Healthy subjects were recruited in response to an advertisement in a local community newspaper. Six healthy Caucasian male subjects were included in the study. Table 1 shows the demographic data. The subjects did not have any clinical significant medical or neurological history, and they did not have any clinically significant abnormality on physical, neurological, or laboratory examinations. In addition, they were not taking any anti-inflammatory medication at the moment of the scan or during at least four weeks before the scan. The study was approved by the local Ethics Committee and conducted according to the latest guidelines of the Declaration of Helsinki. Written informed consent was obtained from all volunteers before the start of their study.

Radiotracer characteristics and preparation [^{11}C]-NE40

Radiotracer preparation was performed as described previously [24]. In short, a stream of helium containing [^{11}C]-CH_3I was bubbled through a solution of 200 µg 2-oxo-7-hydroxy-8-butyloxy-1,2-dihydroquinoline-3-carboxylic acid cyclohexylamide and 2–4 miligram Cs_2CO_3 in 200 µl dimethylformamide. The reaction mixture was heated and diluted. The radiolabeled compound [^{11}C]-NE40 was collected using reversed-phase high performance liquid chromatography (HPLC). After formulation, the identity, chemical and radiochemical purity of the tracer agent [^{11}C]-NE40 were checked using HPLC. Specific activity was 363 (range 200-632) GBq/µmol; the maximum amount of cold NE40 injected was < 1.0 (range 0.4-0.9) µg.

PET/CT procedure

All subjects fasted for at least 6 hours before PET. Subjects underwent a dynamic series of 9 whole-body PET-CT scans on a Hirez Biograph 16 PET/CT (Siemens, Erlangen, Germany) after bolus I.V. injection of 286 MBq (range 201-325 MBq) of [^{11}C]-NE40. Data were acquired with a single energy window set at 425 to 650 keV. The first PET segment (sequential acquisition of WB scan 1 to 8) started simultaneously with the bolus injection and lasted for 60 minutes (time per bed position 30 s (for WB1-3), 60 s (for WB4-6) and 120 s (for WB7-8)). The second segment (WB9) started at 120 minutes post-injection at 4 minutes per bed position. A low-dose CT (tube potential 80 kV; 11 mAs) was performed before each scan segment (The additional effective dose from this CT is 0.5 mSv (CT-Expo version 1.7, male phantom), so the subject underwent an estimated additional radiation burden of 1.0 mSv on top of the PET study). At our center, daily quality control (QC) of the PET system is performed using a uniform ^{68}Ge cylinder to check the uniformity and the stability of the system. Cross calibration with the dose calibrator is performed at least every 3 months using a uniform ^{18}F cylinder [28]. Moreover, we work according to the EARL FDG PET/CT

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accreditation program (ResEARch for Life). (http://earl.eanm.org/cms/website.php?id=/en/projects/fdg_pet_ct_accreditation.htm).

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Whole-body images were reconstructed using a three-dimensional (3D) ordered-subset expectation maximization (OSEM) iterative reconstruction, with 5 iterations and 8 subsets, with CT-based attenuation and scatter correction by standard vendor-based reconstruction. No partial volume effect correction was performed.

Urine was collected after each scan segment for total urinary bladder activity determination and up to 3 hours post injection. Volume was determined by weighing the amount of urine and activity concentration was determined by measuring the activity of a defined volumetric sample of 1 ml with a well counter Wallac 1480 wizard 14 inch (Perkin Elmer, Turku, Finland).

Safety was assessed through physical and neurological examination, vital parameter assessment, electrocardiogram (ECG), laboratory testing, and monitoring of subjective adverse experiences with telephone follow-up 24 hours and 14 days post-injection.

Data Analysis

Data were analyzed and reported accoring to the EANM guidelines for clinical dosimetry reporting [29]. Reconstructed data were analyzed using PMOD software (version 3.0; PMOD Inc., Zurich). Three dimensional VOIs were constructed on the PET emission images to include all organ activity, and their position was verified on corresponding CT images, as described previously [30]. The following organs with significant visualized activity were included as source organs: brain, gallbladder, intestines, heart, kidneys, liver, lungs, red marrow, spleen, thyroid and urinary bladder. Total tracer retention as a function of time or time-activity curves (TACs) was determined. To account for the differences in timing of each bed position, the corresponding acquisition times were calculated for each source organ, taking the bed position of the axial midposition of the organ under consideration on the

corresponding CT scout image on which bed positions with spatial overlap are indicated. Specifically, for the axial red marrow, the midlumbar vertebral position was taken as the average time value. In this way, time-activity curves were calculated for each of the source organs indicated earlier.

To determine preliminary kinetics of brain and spleen uptake, mean standard uptake value (SUV) TACs for brain and spleen were generated.

Organ time-integrated activity coefficients (previously named 'residence times' [31]) were computed by calculating the area under the time-activity curve (TAC) of each source organ through curve fitting. Different models for different organs were used, depending on their kinetics (standardly, a bi-exponential curve was taken when the first data point was already the maximum activity point; in other cases an extra factor or term $(1-\exp(-\ln(2)xT/T_i)$ was included to produce a better fit with a specific maximum). For heart wall, kidneys, spleen and thyroid a bi-exponential was fitted, while a mono-exponential could be used for the lungs. To account for the tracer uptake phase in brain and liver, the function $A_1 \times (1-\exp(-\ln(2)xT/T_1)) \times \exp(-\ln(2)xT/T_2)$ was fitted to the TAC while the function $A_1 \times (1-\exp(-\ln(2)xT/T_1)) \times \exp(-\ln(2)xT/T_2)+A_2 \times \exp(-\ln(2)xT/T_{e3})$ was used to model the TAC of gallbladder, red marrow and remainder.

The ICRP 30 gastrointestinal (GI) model [32] was used to determine the time-integrated activity coefficients for the organs involved in the gastrointestinal tract while the voiding bladder model with a voiding interval of 2 hours was used to estimate the time-integrated activity coefficient for the urinary bladder (UB) [33]. The fraction of injected activity entering the small intestines was estimated by fitting the exponential $A_{GI1}+A_{GI2}\times(1-\exp(-\ln(2)\times T/T_{GI}))$ to the decay corrected TAC of the intestinal VOI. Total fraction for the gastrointestinal tract was determined as $(A_{GI1}+A_{GI2})$ normalized to injected activity A_{inj}. The remaining fraction of

the injected activity was considered as excreted through the urinary bladder. Biological half-life for the fraction entering the urinary bladder was estimated by fitting $(A_{inj}-A_{GI1}-A_{GI2})\times(1-\exp(-\ln(2)\times T/T_{UB}))$ to the TAC of the urinary bladder corrected for decay and between scan voiding. Radiation exposure of the body and critical organs were calculated from the tracer time-integrated activity coefficients using the OLINDA (Organ Level Internal Dose Assessment, Vanderbilt University, USA) software package. The effective dose (ED) was calculated from the individual organ doses with a predefined weighting factor for each of the source organs [34].

Results

As for safety, all monitored clinical parameters (heart rate, blood pressure, 12-lead electrocardiogram, blood analysis) remained normal and no clinically significant adverse experiences were reported by the subjects at the time of scanning, nor were any reported during the follow-up phone interviews.

Figure 1 shows a series of coronal and sagittal whole-body slices of [^{11}C]-NE40 over time for a representative subject. The tracer was readily taken up in the liver and partially excreted through the gastrointestinal system. Some urinary tract activity was noted after a few minutes. Based on the statistics of the abdominal VOI, 10.5±7.5% of the injected activity was entering the intestines and therefore considered as cleared hepatobiliary. The remaining fraction was considered excreted through the urinary tract, with a biological urinary clearance half-life estimated at 183±96 hours. Due to the slow urinary excretion rate**,** collected urinal activity from the first two patients during 3 hours post injection was very limited and therefore was not further taken into account for the calculations. Rapid uptake (to a maximum of 1.5- 3% of the injected activity) and fast washout in the brain was seen, in accordance with the low CB2R expression levels in normal brain.

Figure 2 shows relative time-activity curves for the liver, brain, gallbladder and spleen after injection of [^{11}C]-NE40. The highest variability in activity was observed in the gallbladder. In one of the subjects we observed a second peak of activity after 40 minutes post-injection (p.i.).

Time-integrated activity coefficients for all individual patients and source organs are given in Supplementary Table 1. Table 2 summarizes organ mean radiation absorbed doses and the effective doses. Individual organ absorbed ~~doses~~doses; average organ doses derived from individual doses as well as based on mean kinetic parameters (time-integrated activity coefficient TIAC) and their relative difference (%) are given in Supplemental Table 2. As can be seen from this table, there is only a very small difference between both approaches. The small intestine and the liver showed the highest organ dose of 15.6 and 11.5 µGy/MBq, respectively, followed by the heart wall (7.02 µGy/MBq). Table 1 includes the individual ED estimates for all subjects. The average ED was 3.64 ± 0.81 µSv/MBq (range 2.79 to 5.09 µSv/MBq). No significant correlation between age and ED was found.

Figure 3 shows the time activity curves (standard uptake values, SUV) with activity values corrected for decay caused by the time interval between tracer injection and start time of the different whole body PET scans of the six healthy volunteers for the brain and the spleen. In the brain, a maximum between 10-20 min can be seen in some subjects, with thereafter a continuous decline of the SUV value. In the spleen, after 20 minutes a stable SUV is seen, plateauing around 1.

Discussion

Biomarkers of (neuro)inflammation can be useful as a tool in drug development and in clinical conditions for severity assessement and therapy follow-up. The CB2R is predominantly expressed in peripheral tissues and shows the highest expression levels in

organs of the immune system [35]. In the central nervous system, CB2R is upregulated in inflammatory conditions of activated microglia. Most of the CB2R radioligands described so far are derivatives of 2-oxoquinoline class that have shown a high selectivity for CB2Rs as inverse agonists [22-24, 36-37]. Although some were promising in *in vitro* studies, their *in vivo* stability was poor with fast metabolisation. Proof-of-principle of the feasibility of CB2R imaging in pathological conditions with a neuroinflammatory component in vivo was described by Horti et al. [21]. Since [^{11}C]-NE40 showed favourable characteristics for neuroimaging, we performed this first-in-man study to assess the biodistribution and evaluate the safety of [^{11}C]-NE40.

The gallbladder showed the highest variability in activity. In one of the subjects we observed a second peak of activity after 40 minutes p.i., possibly due to an early contraction of the gallbladder, after which there is an accumulation of the activity with a second contraction. Overall the gallbladder activity can differ between subjects due to large differences in the individual kinetics of gallbladder emptying, a process influenced by multiple hormonal factors and gastrointestinal interactions.

The average injected tracer mass dose in this study was less than 1.0 µgram. There were no subjective effects or adverse events including changes in laboratory blood tests, blood pressure, pulse and ECG. The subjects in this study received a total ED of 2.1 mSv including the PET and attenuation correction CT studies. In a recent literature overview of 32 human PET radiation dosimetry studies with ^{11}C radioligands, van der Aart et al. showed that the vast majority have an effective dose of below 9 µSv/MBq, with a mean of 5.9 µSv/MBq [38]. The effective radiation dose in our study is thus less than this average, moreover indicating that multiple PET scans can be performed in the same subject within conventionally accepted dose limits (class IIA WHO of 10 mSv), allowing its use in drug development and follow-up studies.

Conclusion

[^{11}C]-NE40 results in an effective human radiation dose of 3.64 µSv/MBq, which is in the lower end of the range of ^{11}C- tracers. The biodistribution with spleen uptake and absence of fixed brain uptake in healthy conditions makes the tracer promising for further studies in pathological conditions.

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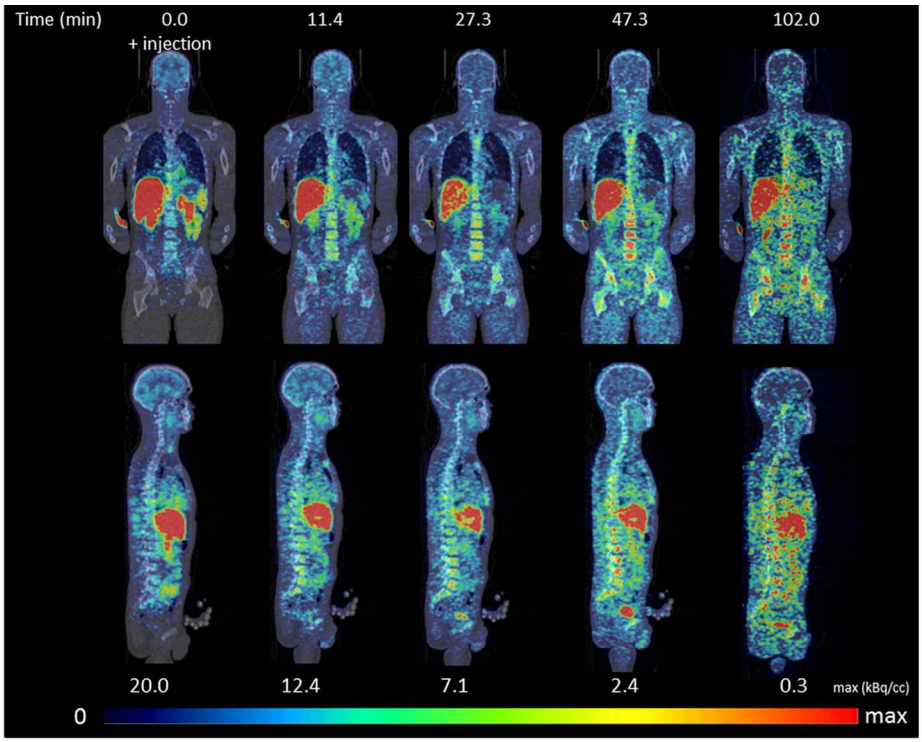
Figure Legends

Figure 1: Whole-body coronal and mid-sagittal PET-CT sections of [^{11}C]-NE40 in subject 2 (uncorrected for decay, in kBq/cc). Data are normalized in the same scale on a maximum activity given in the bottom row, in order to better visualize the relative distribution. Upper row indicates start time (min) of whole-body scan.

Figure 2: Mean activity over time in brain, spleen, liver and gallbladder as fraction of total-body activity for all subjects.

Figure 3: ~~Decay corrected t~~Time activity curves (expressed in standard uptake value (SUV)~~:~~ activity values decay corrected relative to the time of tracer injection) of the spleen and the brain for the 6 volunteers.



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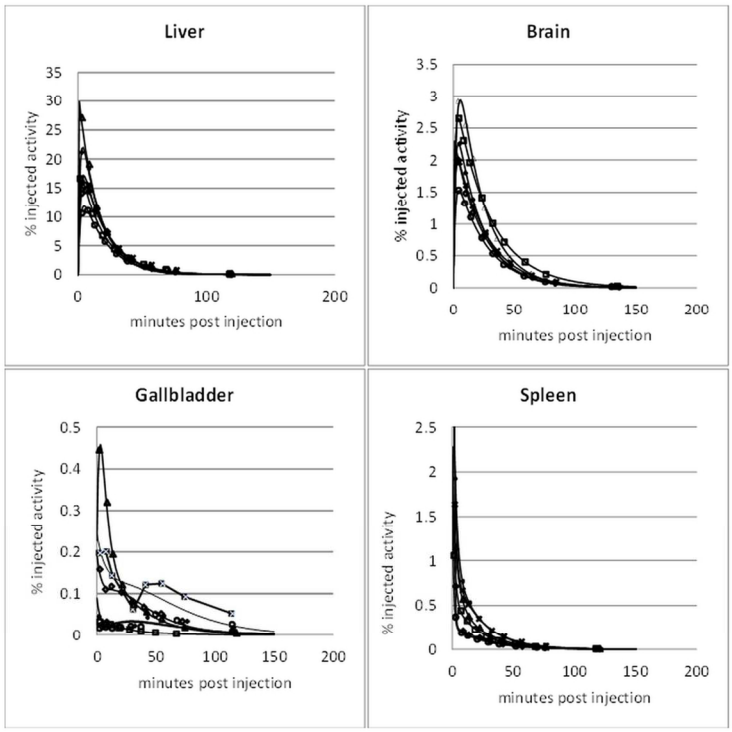

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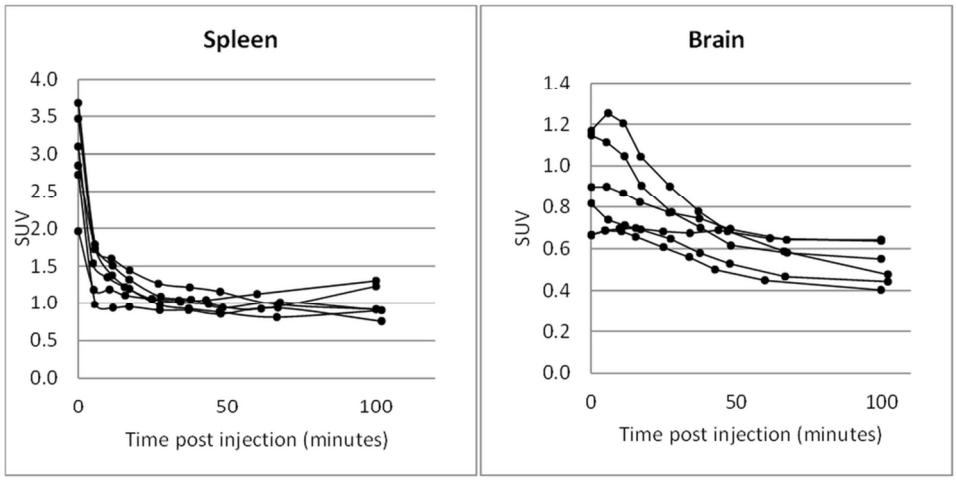

Figure 3: Time activity curves (expressed in standard uptake value (SUV); activity values decay corrected relative to the time of tracer injection) of the spleen and the brain for the 6 volunteers.
114x85mm (300 x 300 DPI)

Table 1. Subject Data, net injected activity of [^{11}C]-NE40, and individual effective dose

Subject	Sex	Age (y)	Height (cm)	Mass (kg)	Body mass index (kg/m²)	Injected activity (MBq)	Individual ED (µSv/MBq)
HV_1	M	20.8	178	61	19.3	302.3	3.93
HV_2	M	44.9	187	90	25.7	201.2	2.79
HV_3	M	24.2	186	86	24.8	254.8	3.05
HV_4	M	65.3	166	61	22.1	310.1	5.09
HV_5	M	61.0	187	90	25.7	324.1	3.46
HV_6	M	22.6	192	82	22.2	325.8	3.54
Mean ± SD		39.8±20.1	182.7±9.3	78.3±13.8	23.3±2.6	286±49	3.64±0.81

HV: healthy volunteer, M: male, y: year, SD: standard deviation, ED: effective dose

Table 2: Radiation absorbed dose estimate (OLINDA) Based on ICRP 30 gastrointestinal tract model

Target Organ	Mean Absorded Dose (μGy/MBq)	Coefficient of variation (%)
Adrenals	2.71 ± 0.394	14.1
Brain	2.73 ±0.84	30.7
Breasts	1.547 ± 0.293	20.1
Gallbladder Wall	5.82 ± 0.13	21.8
Lower Large Intestine Wall	2.62 ± 0.10	38.8
Small Intestine	15.6 ± 1.03	65.7
Stomach Wall	2.263 ± 0.514	22.8
Upper large intestine Wall	6.657 ± 3.83	57.6
Heart Wall	7.02 ± 2.273	32.4
Kidneys	6.657 ± 1.53	23.0
Liver	11.5 ± 1.152	10.0
Lungs	4.01 ± 0.697	17.2
Muscle	1.758 ± 0.41	23.4
Pancreas	2.72 ± 0.43	15.8
Red Marrow	5.071 ± 0.93	18.4
Osteogenic Cells	4.283 ± 1.00	23.4
Skin	1.31 ± 0.31	23.5
Spleen	6.01 ± 1.31	21.8
Testes	1.42 ± 0.364	25.2
Thymus	1.768 ± 0.34	19.3
Thyroid	4.283 ± 1.32	30.9
Urinary Bladder Wall	2.44 ± 0.768	31.2
Uterus	2.768 ± 1.10	39.7
Total Body	2.40 ± 0.51	21.3
Effective dose (μSv/MBq)	3.64E ± 0.81	22.3

Data are mean ± SD

(SUPPLEMENTAL TABLES)

Whole-body biodistribution and radiation dosimetry of the cannabinoid type 2 receptor ligand [^{11}C]-NE40 in healthy subjects

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Supplemental Table 1: Time-integrated activity coefficients ('residence times' – in hours) for the individual subjects, as obtained by multiexponential curve fitting

Subject Nr.	1	2	3	4	5	6	mean	SD
Brain	0.0145	0.0095	0.0136	0.0077	0.0098	0.0098	0.0108	0.002638
Gallbladder	0.0002	0.0011	0.0015	0.0006	0.0006	0.0019	0.0010	0.000647
Lower Large Intestine	0.0001	0.0001	0.0001	0.0005	0.0002	0.0002	0.0002	0.000155
Small Intestines	0.0320	0.0217	0.0301	0.1116	0.0413	0.0385	0.0459	0.032927
Upper Large Intestine	0.0038	0.0026	0.0036	0.0132	0.0049	0.0045	0.0054	0.003887
Heart Wall	0.0042	0.0139	0.0074	0.0077	0.0060	0.0052	0.0074	0.003422
Kidneys	0.0046	0.0046	0.0065	0.0048	0.0057	0.0096	0.0060	0.001956
Liver	0.0613	0.0660	0.0819	0.0499	0.0729	0.0699	0.0670	0.010863
Lungs	0.0099	0.0099	0.0113	0.0128	0.0140	0.0136	0.0119	0.001817
Red Marrow	0.0275	0.0373	0.0310	0.0335	0.0380	0.0361	0.0339	0.004057
Spleen	0.0026	0.0051	0.0032	0.0014	0.0048	0.0046	0.0036	0.001467
Thyroid	0.0002	0.0002	0.0003	0.0003	0.0006	0.0003	0.0003	0.000151
Urinary Bladder	0.0011	0.0006	0.0013	0.0015	0.0004	0.0007	0.0009	0.000432
Remainder	0.2569	0.2217	0.2014	0.2304	0.2033	0.2146	0.2214	0.020578

Supplemental table 2: Individual organ doses (OLINDA) (mGy/MBq) for the 6 subjects (as defined in Table 1) of the study, and average organ doses derived from individual doses as well as based on mean kinetic parameters (time-integrated activity coefficients (TIAC)) and their relative difference (%).

Subject Nr.	1	2	3	4	5	6
Adrenals	3.21E-03	2.38E-03	2.47E-03	3.18E-03	2.38E-03	2.64E-03
Brain	4.31E-03	2.11E-03	2.97E-03	2.47E-03	2.15E-03	2.34E-03
Breasts	1.89E-03	1.31E-03	1.25E-03	1.80E-03	1.22E-03	1.35E-03
Gallbladder Wall	4.50E-03	5.36E-03	6.66E-03	6.21E-03	4.49E-03	7.68E-03
LLI Wall	2.91E-03	1.88E-03	1.93E-03	4.55E-03	2.14E-03	2.31E-03
Small Intestine	1.22E-02	8.05E-03	1.05E-02	3.62E-02	1.37E-02	1.32E-02
Stomach Wall	2.71E-03	1.89E-03	1.88E-03	3.08E-03	1.89E-03	2.09E-03
ULI Wall	5.92E-03	3.80E-03	4.65E-03	1.43E-02	5.61E-03	5.61E-03
Heart Wall	5.65E-03	1.06E-02	6.45E-03	9.05E-03	5.25E-03	5.13E-03
Kidneys	6.62E-03	4.73E-03	6.42E-03	7.25E-03	5.64E-03	9.22E-03
Liver	1.31E-02	9.95E-03	1.26E-02	1.12E-02	1.09E-02	1.14E-02
Lungs	4.26E-03	3.12E-03	3.49E-03	5.11E-03	3.90E-03	4.15E-03
Muscle	2.21E-03	1.47E-03	1.45E-03	2.33E-03	1.44E-03	1.60E-03
Ovaries	3.28E-03	2.07E-03	2.20E-03	5.39E-03	2.40E-03	2.58E-03
Pancreas	3.21E-03	2.39E-03	2.42E-03	3.31E-03	2.37E-03	2.62E-03
Red Marrow	5.63E-03	4.50E-03	4.13E-03	6.67E-03	4.59E-03	4.89E-03
Osteogenic Cells	5.40E-03	3.64E-03	3.40E-03	5.70E-03	3.60E-03	3.96E-03
Skin	1.73E-03	1.11E-03	1.09E-03	1.67E-03	1.06E-03	1.19E-03
Spleen	5.85E-	7.16E-	5.05E-	3.97E-	6.82E-	7.23E-

	03	03	03	03	03	03			
Testes	1.92E-03	1.21E-03	1.15E-03	1.83E-03	1.13E-03	1.28E-03			
Thymus	2.22E-03	1.63E-03	1.49E-03	2.15E-03	1.45E-03	1.60E-03			
Thyroid	3.83E-03	2.65E-03	3.70E-03	5.14E-03	6.43E-03	3.90E-03			
Urinary Bladder Wall	3.05E-03	1.85E-03	2.29E-03	3.67E-03	1.72E-03	2.08E-03			
Uterus	3.12E-03	1.95E-03	2.07E-03	4.84E-03	2.21E-03	2.39E-03			
Total Body	2.87E-03	1.99E-03	2.06E-03	3.20E-03	2.04E-03	2.23E-03			
ED	0.00393	0.00279	0.00305	0.00509	0.00346	0.00354			
Subject Nr.	1	2	3	4	5	6	mean absorbed dose	organ doses from mean TIAC	relative difference
Adrenals	3.21E-03	2.38E-03	2.47E-03	3.18E-03	2.38E-03	2.64E-03	2.71E-03	2.78E-03	2.52%
Brain	4.31E-03	2.11E-03	2.97E-03	2.47E-03	2.15E-03	2.34E-03	2.73E-03	2.79E-03	2.33%
Breasts	1.89E-03	1.31E-03	1.25E-03	1.80E-03	1.22E-03	1.35E-03	1.47E-03	1.51E-03	2.65%
Gallbladder Wall	4.50E-03	5.36E-03	6.66E-03	6.21E-03	4.49E-03	7.68E-03	5.82E-03	5.95E-03	2.24%
LLI Wall	2.91E-03	1.88E-03	1.93E-03	4.55E-03	2.14E-03	2.31E-03	2.62E-03	2.64E-03	0.76%
Small Intestine	1.22E-02	8.05E-03	1.05E-02	3.62E-02	1.37E-02	1.32E-02	1.56E-02	1.57E-02	0.37%
Stomach Wall	2.71E-03	1.89E-03	1.88E-03	3.08E-03	1.89E-03	2.09E-03	2.26E-03	2.30E-03	1.88%
ULI Wall	5.92E-03	3.80E-03	4.65E-03	1.43E-02	5.61E-03	5.61E-03	6.65E-03	6.64E-03	-0.13%
Heart Wall	5.65E-03	1.06E-02	6.45E-03	9.05E-03	5.25E-03	5.13E-03	7.02E-03	7.40E-03	5.11%
Kidneys	6.62E-03	4.73E-03	6.42E-03	7.25E-03	5.64E-03	9.22E-03	6.65E-03	6.96E-03	4.50%
Liver	1.31E-02	9.95E-03	1.26E-02	1.12E-02	1.09E-02	1.14E-02	1.15E-02	1.21E-02	4.75%
Lungs	4.26E-03	3.12E-03	3.49E-03	5.11E-03	3.90E-03	4.15E-03	4.01E-03	4.14E-03	3.26%
Muscle	2.21E-03	1.47E-03	1.45E-03	2.33E-03	1.44E-03	1.60E-03	1.75E-03	1.78E-03	1.69%
Ovaries	3.28E-03	2.07E-03	2.20E-03	5.39E-03	2.40E-03	2.58E-03	2.99E-03	3.00E-03	0.44%

Pancreas	3.21E-03	2.39E-03	2.42E-03	3.31E-03	2.37E-03	2.62E-03	2.72E-03	2.78E-03	2.16%
Red Marrow	5.63E-03	4.50E-03	4.13E-03	6.67E-03	4.59E-03	4.89E-03	5.07E-03	5.24E-03	3.28%
Osteogenic Cells	5.40E-03	3.64E-03	3.40E-03	5.70E-03	3.60E-03	3.96E-03	4.28E-03	4.40E-03	2.65%
Skin	1.73E-03	1.11E-03	1.09E-03	1.67E-03	1.06E-03	1.19E-03	1.31E-03	1.33E-03	1.63%
Spleen	5.85E-03	7.16E-03	5.05E-03	3.97E-03	6.82E-03	7.23E-03	6.01E-03	6.45E-03	6.77%
Testes	1.92E-03	1.21E-03	1.15E-03	1.83E-03	1.13E-03	1.28E-03	1.42E-03	1.45E-03	2.07%
Thymus	2.22E-03	1.63E-03	1.49E-03	2.15E-03	1.45E-03	1.60E-03	1.76E-03	1.80E-03	2.41%
Thyroid	3.83E-03	2.65E-03	3.70E-03	5.14E-03	6.43E-03	3.90E-03	4.28E-03	4.31E-03	0.81%
Urinary Bladder Wall	3.05E-03	1.85E-03	2.29E-03	3.67E-03	1.72E-03	2.08E-03	2.44E-03	2.44E-03	-0.14%
Uterus	3.12E-03	1.95E-03	2.07E-03	4.84E-03	2.21E-03	2.39E-03	2.76E-03	2.78E-03	0.60%
Total Body	2.87E-03	1.99E-03	2.06E-03	3.20E-03	2.04E-03	2.23E-03	2.40E-03	2.46E-03	2.51%
ED	0.00393	0.00279	0.00305	0.00509	0.00346	0.00354	0.003643	0.00387	5.86%