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# A Phase 1 and Biodistribution Study of ABT-806i, An Indium-111 Radiolabeled Conjugate of the Tumor-Specific Anti-EGFR Antibody ABT-806

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**Running title:** Phase I Study of ABT-806i against EGFR

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**Abstract (283 words)**

ABT-806 is a tumor-specific antibody targeting the epidermal growth factor receptor (EGFR). This study assessed safety, biodistribution and pharmacokinetics of indium-111 ($^{111}$In) radiolabeled ABT-806 (ABT-806i) and effects of repeated doses of ABT-806 on receptor occupancy.

**Methods**: Eligible patients had advanced tumors likely to express EGFR/EGFRvIII; adequate performance status and organ function; and measurable disease by RECIST 1.1. In Cohort 1, 6 patients received a bolus administration of ABT-806i and underwent single-photon emission computed tomography (SPECT) followed by whole body planar scans. In Cohort 2, 12 patients were imaged similarly as in 1 initially; thereafter they received three doses of unlabelled ABT-806, before another dose of ABT-806i with associated SPECT and whole body planar scans. At the end of both cohorts, patients who had stable or responding disease were able to enroll into an extension study (M12-326) where they received unlabelled ABT-806 every 2 weeks until disease progression, withdrawal of consent or intolerable toxicity

**Results**: No toxicity related to ABT-806i infusion were observed. ABT-806i showed minimal uptake in normal tissues and cleared gradually from blood with $t_{½}$ of 6.0 $\pm$ 1.5 days. The mean effective dose of ABT-806i was determined as 0.137 mSv/MBq for males and 0.183 mSv/MBq for females. ABT-806i tumor uptake varied and did not correlate with archived tumor EGFR expression. No change in ABT-806i uptake was observed after interval ABT-806 treatment, indicating stable EGFR expression in tumor. The patient with highest tumor uptake of ABT-806i had advanced head and neck cancer and experienced a partial response.

**Conclusion**: ABT-806i allows for real-time imaging of EGFR conformational expression in tumors, has an acceptable radiation dosimetry and provides important additional information about

antigen expression compared to standard approaches using archival tissue. Its role to assist in patient selection for EGFR-based therapeutics and investigate treatment resistance should be further investigated.

**Keywords:** EGFR, EGFRvIII, Solid Tumors, SPECT Imaging, Biodistribution

## Introduction

The *Epidermal Growth Factor Receptor* (*EGFR*) gene is a validated target in oncology. Monoclonal antibodies against EGFR are used to treat cancers of the head and neck, colon and lung (*1,2*). Tyrosine kinase inhibitors of EGFR are used in the treatment of lung cancer with activating kinase mutations (*1,2*). The most common toxicity of these agents is a well-characterized skin rash (*3*). Other toxicities include diarrhea, stomatitis, fatigue, and electrolyte disturbances.

ABT-806 is a humanized recombinant IgG1κ antibody that is specific for a unique, conformationally exposed epitope of EGFR. This epitope is available for binding only under conditions where there is dysregulated EGFR activation due to conditions such as EGFR amplification, presence of specific mutations such as EGFRde2-7 (EGFRvIII) or presence of autocrine loops (*1,4-6*). The epitope is inaccessible when EGFR is expressed at normal physiological levels, thus ABT-806 has limited binding to normal tissues (*1,4-6*). ABT-806 reproducibly inhibits the growth of multiple EGFR amplified/EGFRvIII mutated tumors pre-clinically through down-regulation of EGFR signaling with result anti-tumor changes in proliferation, angiogenesis and apoptosis (*1,7-9*). When compared to other EGFR-directed therapies, preclinical studies show ABT-806 has a favorable toxicity profile and equivalent/improved efficacy to other anti-EGFR antibodies (*1,8,10,11*). In a Phase 1 human study of ABT-806 (Study M11-847, NCT01255657), the recommended Phase 2 dose (RPTD) was 24 mg/kg (*12*). Importantly, ABT-806 was shown to have negligible skin or other organ toxicity (*12,13*).

ABT-806i, an indium-111 radiolabeled conjugate of ABT-806, is a novel radiopharmaceutical which was developed for real time scintigraphic imaging of EGFR. It utilizes

the tumor-specific binding affinity of ABT-806 for the imaging of EGFR-positive tumors to determine if EGFR amplification, overexpression or mutation is present. We report herein the results of a first-in-human trial of ABT-806i, exploring the ability to image the conformational epitope of EGFR bound by ABT-806, the impact of ABT-806 therapy on ABT-806i uptake, and the relationship of ABT-806i uptake to tumor EGFR by immunohistochemistry (IHC).

## Materials and Methods

### *Trial Objectives*

This first-in-human trial (M11-849, NCT01472003) was a two-cohort, open label, multi-center study to determine the biodistribution and dosimetry of ABT-806i. Secondary objectives included characterization of ABT-806i pharmacokinetics (PK); examination of ABT-806i SPECT imaging in tumors of different histologies, EGFR expression and size; and determining the effect of unlabelled ABT-806 on ABT-806i receptor occupancy. The study was approved by the Austin Health Human Research Ethics Committee and all subjects signed an informed consent form.

### *Patient Eligibility for M11-849 Bioimaging Study*

Eligible patients were aged ≥ 18 years; had tumors of a type likely to overexpress wild-type EGFR/EGFRvIII; were Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2; had measurable disease by RECIST version 1.1 with at least one extrahepatic 2 cm lesion; had adequate organ function, defined as absolute neutrophil count ≥ 1500/$mm^3$; platelets ≥ 100,000/$mm^3$; hemoglobin ≥ 9.0 g/dL; creatinine ≤ 1.5 times the upper limit of the institution's normal range (xULN); bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≤ 1.5 x ULN (those with liver metastases were eligible if their AST and ALT was ≤ 5.0 x

ULN). Exclusion criteria included anticancer therapy within 14 days of the first ABT-806i dose; prior use of EGFR-directed monoclonal antibody within 4 weeks of the first ABT-806i dose; presence of unresolved Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or higher toxicity from prior therapy; major surgery within 21 days prior to the first ABT-806i dose; significant comorbidities which posed an unacceptable risk of toxicities; history of major immunologic reaction to any IgG containing agent; and pregnancy or lactating patients.

*Radiolabelling of ABT-806i*

ABT-806i was formed by mixing a formulated precursor, DTPA-ABT-806, with commercially available indium-111 trichloride. DTPA-ABT-806 was produced from the conjugation of ABT-806 with the isothiocyanate of the phenylisothiocyanate derivative of dientylene triamine pentacetic acid (CHX-A"-DTPA). An average of 2-3 CHX-A"-DTPA moieties were conjugated per antibody. For radiolabeling, 0.5M sodium acetate (pH 7.2, 1.0 mL) was added to indium-111 trichloride (5-7.5 mCi), and then placed in a sterile reaction vial. DTPA-ABT-806 (amount 5mg/2ml) was added to the reaction vial at room temperature, and after mixing was withdrawn into a 5 ml syringe. The total reaction time was 30 minutes. Preclinical studies confirmed retention of binding affinity after radiolabeling (immunoreactive fraction >65%), radiochemical purity >90%, and serum stability studies showed retention of immunoreactivity (data not shown).

*Trial Design of M11-849 study*

Patients were treated as in Figure 1. Patients in Cohort 1 received a single IV administration of ABT-806i to determine baseline drug distribution. Pre-dose scintigraphic scanning with cobalt-

57 transmission (including whole body planar and SPECT) were performed on day 1 prior to bolus administration of ABT-806i (a protein tracer dose of 3-5 mg labelled with 4-7 mCi (148-259 MBq) of indium) preceded approximately 30 minutes prior by 500-1000 mg acetaminophen and 25-50 mg IV promethazine. We and others have previously demonstrated that this dose of $^{111}$In (4-7 mCi) is optimal for diagnostic and dosimetric analysis of intact antibodies (*13-15*). Post-ABT-806i administration, patients underwent whole body planar and SPECT scans on days 1, 2, 3 or 4, 5 or 6, and then on day 7. Thereafter, all patients were eligible to enrol on the extension study (Study M12-326, NCT01406119), which is described below.

In Cohort 2, patients underwent an initial week of imaging for the purposes of determining the biodistribution of ABT-806i, in a manner similar to patients treated on Cohort 1. In this first week, they received ABT-806i (4-7 mCi (148-259 MBq)/3-5 mg) on Day 1 of week 1; this was then followed by whole body planar and SPECT scans on days 1, 3 or 4, 5 or 6, and then on day 7. Beginning on day 1 of week 2, they were treated with either 18 mg/kg or 24 mg/kg of unlabelled ABT-806 every fortnight (weeks 2, 4 and 6); in week 6, they also underwent repeat imaging with another dose of ABT-806i after the unlabelled ABT-806 to determine the effects of unlabelled antibody on receptor occupancy. Imaging after this dose of ABT-806i was on days 2 or 3, 4 or 5, and then day 7 of week 6. At the end of the 6 weeks, all patients with disease response or control were eligible to enrol on the extension study (Study M12-326, NCT01406119).

The (M12-326, NCT01406119) was an extension study to allow patients on the bioimaging study above (M11-849) who had completed the required imaging and had not progressed to continue treatment with unlabelled ABT-806 until withdrawal of consent, disease progression, need for other cancer therapy or intolerable toxicity.

*Pharmacokinetics during M11-849 study*

Pharmacokinetic samples for ABT-806i and ABT-806 were collected prior to dosing and up to 168 hours post dosing on day 1 of week 1 (Cohorts 1 and 2) and up to 336 hours post dosing on day 1 of week 6 (Cohort 2 only). These were measured using the same validated electrochemiluminescence immunoassay and analysed using noncompartmental methods (*16*). Serum samples for antibody drug antibody (ADA) were collected prior to dosing on week 1, day 1 and at the end of study.

*Biodistribution and Dosimetry during M11-849 study*

From whole-body planar and SPECT images, qualitative analysis of the distribution of ABT-806i in the body and tumor uptake was assessed. Tumor uptake in defined target lesions was evaluated on a four-point scale, with comparison of tumor uptake between initial trace infusion of ABT-806i, and following the second infusion of ABT-806i, to evaluate alteration in EGFR expression following ABT-806 treatment, as well as to define possible receptor occupancy with ABT-806 treatment. The quantitative analysis of ABT-806i in normal tissues was determined in the patients in Cohort 1 after injection of ABT-806i by Region of Interest (ROI) technique. Radioactivity as percentage of injected dose per organ (%ID) was measured in various organs of the patients at 5 time points over 7 days (approximately 168 hours) post-injection. For each patient the %ID values of each organ were plotted against time to generate organ biokinetics to obtain organ radiation exposure (*17*).

Tumor uptake of ABT-806i was measured based on SPECT imaging before and after ABT-806 treatment and plotted against time. Target lesions were selected based on tumor size, with minimum size of approximately 2 cm in the longest transverse diameter on computerized

tomography (CT), and sufficient tumor-to-background ratio, ideally greater than approximately 1.5. A major vessel or the heart, selected based on the anatomy in the field of view (FOV), was chosen as the blood pool ROI to estimate radioactivity in the whole blood at the time of imaging (*14*).

*Adverse events during M11-849 study*

Analyses of toxicity included only treatment-emergent adverse events (TEAEs) in the first 30 days after first dose of ABT-806i. TEAEs were summarized by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of toxicity was assessed using NCI CTCAE Version 4.0 toxicity.

*Sample size of M11-849 study*

A pragmatic sample size of 26-30 patients was chosen, with 6 patients in Cohort 1 and the rest in Cohort 2. The study was terminated after 18 patients as sufficient data had been gathered with tolerability of highest available dose. Summary statistics for demographics are provided in Table 1.

**Results**

*Patients*

Patient demographics are shown in Table 1. The first 6 patients were imaged in Cohort 1 and then proceeded immediately to treatment with the ABT-806 on the M12-326 extension study

(Figure 1 and Table 2). In Cohort 2, 6 patients were treated at the 18 mg/kg dose level, and 6 patients at the 24 mg/kg dose level. At the end of Cohort 2, 5/12 patients had stable disease (SD) with formal MRI restaging at the end of the imaging study and proceeded to the M12-326 extension study (Figure 1 and Table 2). Of these, 1 patient in Cohort 2 with SCCHN experienced partial response (Patient 8, Table 2). In total, 11 out of the 18 patients on the M11-849 biodistribution study had stable or better disease at the end of the study and were screened for enrolment in the M12-326 extension study (Table 2).

*Biodistribution of ABT-806i in the M11-849 Biodistribution Study*

Evaluation of imaging datasets showed initial pooling of ABT-806i in the cardiac blood pool and within large vessels, liver, spleen and kidneys, followed by gradual blood clearance and washout of ABT-806i from normal tissues over the 8 days of imaging in all patients (Figure 2). In the patients with uptake of ABT-806i in tumor, this was best seen after day 3 with increasing intensity up to day 8 (Figure 2). High, specific uptake of ABT-806i in tumor was visualized in the target lesions for 5/6 patients in Cohort 1 with the other patients having uptake. High specific uptake was seen in all 12 patients in Cohort 2. The uptake of ABT-806i was observed to peak at the $7^{th}$ or $8^{th}$ day post-injection. Interestingly, both patients with primary brain tumors showed excellent ABT-806i uptake (Figure 2). Furthermore, the increasing accumulation of ABT-806i over time in tumor (maximal uptake around 4 days), despite decline in serum concentration of ABT-806i during this timeframe, would support specific uptake in the glioblastoma tumors imaged in the study. The peak uptake of ABT-806i in target tumor volumes in Cohort 1 and 2 are shown in Tables 3 and 4 respectively.

*Pharmacokinetics during the M11-849 Biodistribution Study*

ABT-806i pharmacokinetics were similar between Cohorts 1 and 2 (Table 5 and Figure 3). The apparently shorter observed half-life and higher clearance of ABT-806i compared to ABT-806 (Figure 3) may be due to a shorter pharmacokinetic sampling period for ABT-806i, although nonlinear pharmacokinetics between the low ABT-806i and high ABT-806 doses cannot be completely excluded. The biodistribution images did not indicate any saturable normal tissue compartment, which would be seen if a nonlinear PK at low protein dose did exist. The ABT-806 pharmacokinetics were consistent with results in the previous Phase 1 dose escalation study with ABT-806. No ADA was detected post-ABT-806 administration in this study.

*Toxicity within M11-849 study*

No patient in the M11-849 study experienced an adverse event related to ABT-806i. Two patients (33%) in Cohort 1 of M11-849 study each experienced an unrelated adverse event of Grade 1 upper respiratory tract infection and Grade 2 dyspnoea. Ten patients (83%) in Cohort 2 experienced toxicity. One patient in Cohort 2 (8%) experienced Grade 1 rash that the investigator considered possibly related to ABT-806 but no toxicities related to ABT-806i were reported. Toxicity occurring in ≥ 2 patients in Cohort 2 included decreased appetite, fatigue (4 patients each, 33.3%), constipation, nausea, upper respiratory tract infection (3 patients each, 25%), arthralgia, dizziness, and productive cough (2 patients each, 17%) that were unrelated. Two of 10 patients each experienced 2 Grade 3 events; the remaining 8 patients experienced Grade 1 or 2 events.

*Tumor uptake and Dosimetry of ABT-806i*

ABT-806i tumor uptake was quantitatively evaluated for patients in Cohorts 1 and 2 (n=18). Tumor uptake varied greatly between patients, and ranged from 0.009-5.837% injected dose for a reference lesion. The only non-tumor region that showed specific ABT-806i uptake was

in patient 1, who had uptake in an area of previous lung radiotherapy, most likely related to enhanced permeability into the area of inflammation. No clear pattern between ABT-806i uptake and EGFR staining in archival tissue was seen (Table 2), although the median interval between tissue acquisition and enrolment on study was 1.5 years (range, 0.3-6.5 years), and archived samples tested were typically from previously removed primary tumors. Repeated treatment with ABT-806 had little effect on ABT-806i tumor accumulation irrespective of ABT-806 dose.

On a per target lesion basis, there were 12 lesions in Cohort 1 of which 7 lesions demonstrated qualitative uptake of ABT-806i, , 2 lesions with mild uptake score of 2; 3 lesions with moderate uptake score of 3; and 2 lesions with marked uptake score of 4. There was 1 target lesion with no uptake (score 0), 1 lesion with equivocal uptake, and 1 lesion with non-evaluable uptake. In Cohort 2, there were 34 lesions, of which 21 lesions had uptake of ABT-806i, including 14 lesions with moderate uptake score of 3, and 1 lesion with marked uptake score of 4. Importantly, of the 13 patients who had more than one evaluable lesion, 4 patients (31%) showed marked inter-tumoral variation of uptake of ABT-806i in target lesions. The patient who had a partial response had high (score 3) uptake of ABT-806i (Figure 4).

The normal tissue dosimetry of ABT-806i is shown in Supplementary Table 1. The mean effective dose of ABT-806i was calculated to be 0.137 mSv/MBq for males and 0.183 mSv/MBq for females.

**Discussion**

The advent of next-generation antibodies like ABT-806 represents the next wave of EGFR-targeting antibodies with enhanced tumor specificity and minimal cutaneous toxicities (*1,7,12,13*). ABT-806 has been shown to be well-tolerated and to have little of the cutaneous and other

toxicities seen with other anti-EGFR antibodies (*12*). Our current study confirmed this profile with only 1 patient (6%) experiencing a Grade 1 rash that was possibly related to ABT-806. Like other anti-EGFR antibodies that have shown some activity in head and neck cancer (*18*), there was one patient with head and neck cancer who had a prolonged objective response.

Administration of ABT-806i was safe and well-tolerated, with no drug-related toxicities. The lung is the organ that had the highest dosimetry for ABT-806i, although the dose received from a tracer infusion of ABT-806i is well within acceptable levels, and consistent with other $^{111}$In-labeled antibodies (*15,19*). In comparison to imaging of wtEGFR, using $^{111}$In-225 (*20*) and $^{89}$Zr-cetuximab (*21*), ABT-806i showed less liver uptake on imaging, with dosimetry and linear pharmacokinetics at low protein doses consistent with lack of normal tissue "sink" as well as tumor-specific EGFR imaging. This imaging illustrated several key observations. Firstly, marked inter-tumoral heterogeneity exists in nearly a third of patients between different metastatic sites. Secondly, it is not possible to predict this inter-tumoral heterogeneity with EGFR testing using archival tissue (or likely even with prospective tissue collection from single tumor sites). Lastly, the observation that the one responder in this study also had the higher ABT-806i uptake suggests a possible use to enrich for patients who will respond to anti-EGFR treatment. Clearly, our results require further validation given the relatively small study size and the heterogeneous patient population. However, the possibility that prospective and contemporaneous assessment of antigen target expression using radiolabeled tracers may impact on patient selection for antibody-based therapeutics has been shown by other trials, including T-DM1 (*22*) and may have an important role in drug development (*14,23*). Arguably, ABT-806i imaging could present way to enrich for responders for therapy with ABT-414, which comprised of ABT-806 conjugated to monomethyl auristatin F (MMAF)(*24*). Using selection on EGFR amplification in archival tissue, adding ABT-

414 to standard post-operative chemo-radiation did not improve survival in newly diagnosed patients (*25*) but there was a trend, though not statistically significant, toward survival benefit when combining ABT-414 with temozolomide in patients with recurrent GBM (*26*). In both studies, the need for better patient selection for highly targeted drugs like ABT-414 was emphasized (*25,26*) and imaging with ABT-806i could represent one way to do so.

**Conclusion**

In conclusion, this study has established the safety and feasibility of molecular imaging of intra-tumoural EGFR expression using ABT-806i scanning and illustrates possible roles in the development of antibody-based therapeutics.

## Disclosures

### Conflict of Interest Disclosures

**HKG:** received honoraria, travel support and/or research funding from AbbVie, BMS, Eisai, EMD Serono and MSD.

**MB:** served on advisory boards and received honoraria from Roche, Amgen and Sirtex

**BS:** served on advisory boards and received honoraria from Pfizer, Merck, Roche-Genetech, AstraZeneca, Bristol-Myers Squibb and Novartis

**STL:** Nil

**KDH, WM, JF, PA, GF, HX, EBR and RH:** Employees of AbbVie and may own stock

YZ: Previous AbbVie employee and may own stock

**MC:** Employee of Bristol-Myers Squibb and may own stock

**AMS:** Received research funding and travel support from AbbVie; received research funding from Daiichi-Sankyo, Merck, Telix, Avid, Celgene, ITM; is a consultant and has stock in Life Science Pharmaceuticals

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**Key Points**

1) We confirmed the safety of ABT-806i and acceptable radiation dosimetry
2) We demonstrate the ability to successfully obtain real-time imaging of EGFR conformational expression in tumors
3) Our data provides support for the use of theranostics to guide patient selection for EGFR-targeting therapies

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**Figures**

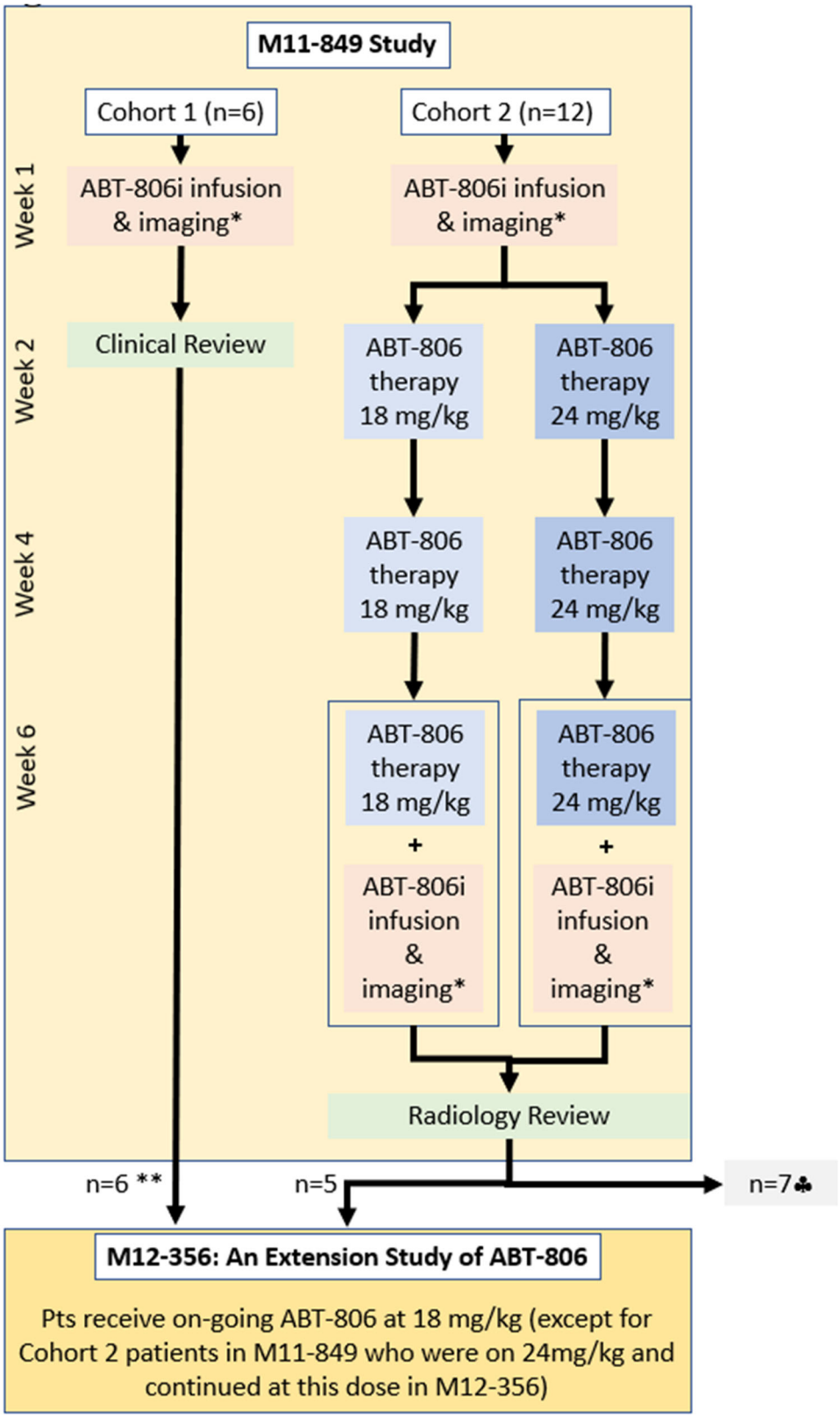
M11-849 Study
Cohort 1 (n=6)
Cohort 2 (n=12)
Week 1
ABT-806i infusion & imaging*
ABT-806i infusion & imaging*
Week 2
Clinical Review
ABT-806 therapy 18 mg/kg
ABT-806 therapy 24 mg/kg
Week 4
ABT-806 therapy 18 mg/kg
ABT-806 therapy 24 mg/kg
Week 6
ABT-806 therapy 18 mg/kg
+
ABT-806i infusion & imaging*
ABT-806 therapy 24 mg/kg
+
ABT-806i infusion & imaging*
Radiology Review
n=6 **
n=5
n=7♣
M12-356: An Extension Study of ABT-806
Pts receive on-going ABT-806 at 18 mg/kg (except for Cohort 2 patients in M11-849 who were on 24mg/kg and continued at this dose in M12-356)

**Figure 1. Patient Flow within M11-849 study and subsequently for eligible patient, from the M11-849 study into the M12-356 extension study**

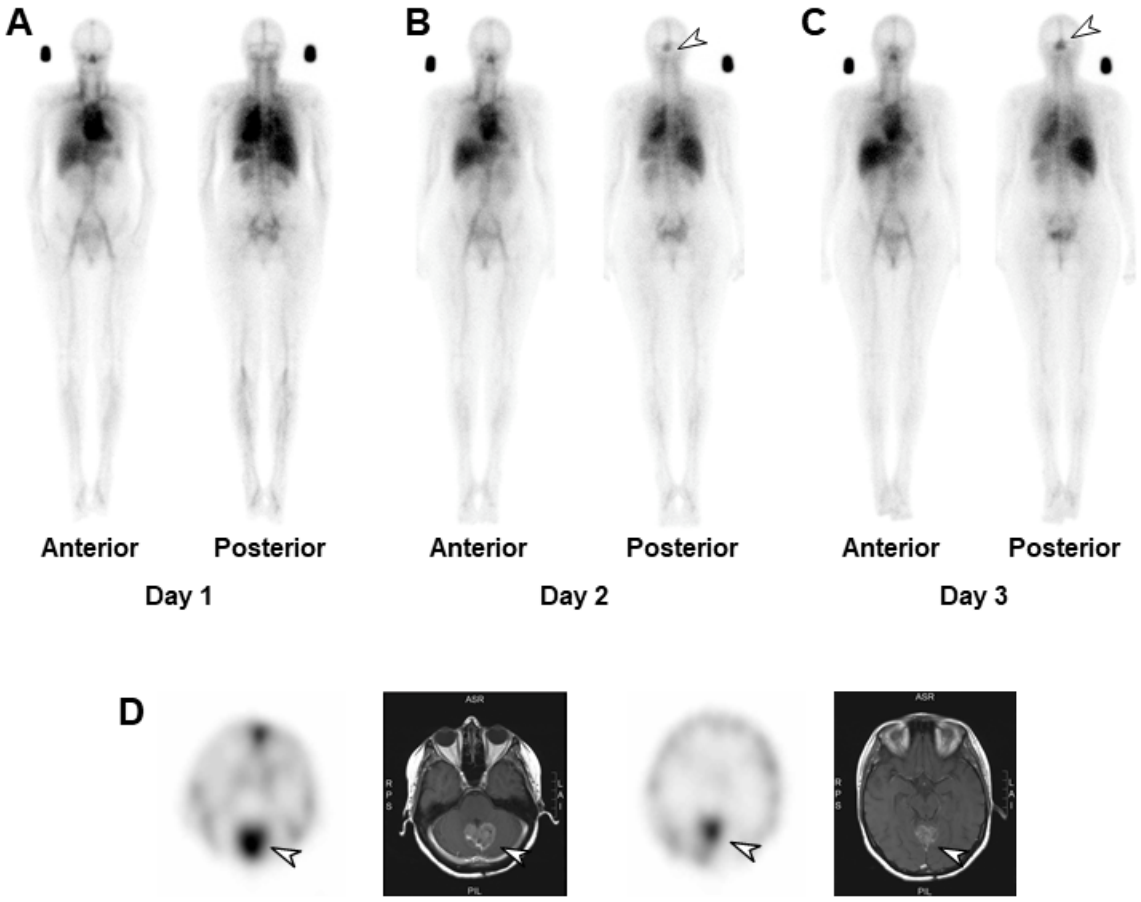


**Figure 2. ABT-806i biodistribution and SPECT/CT images of a patient with high grade glioma.** (**A**) Anterior and posterior whole body planar images at day 1 (standard located above right shoulder for dosimetry); (**B**) whole body planar images at day 2; (**C**) whole body planar images at day 3 in patient 3. Rapid uptake of $^{111}$In-ABT-806i in known GBM (arrow) is identified by day 2 and increases by day 3. (**D**) SPECT/MRI images at two planes showing the high uptake of $^{111}$In-ABT-806i in the GBM (arrow) in the posterior fossa. A focus of $^{111}$In-ABT-806i uptake in the anterior venous sinus is due to blood pool activity.

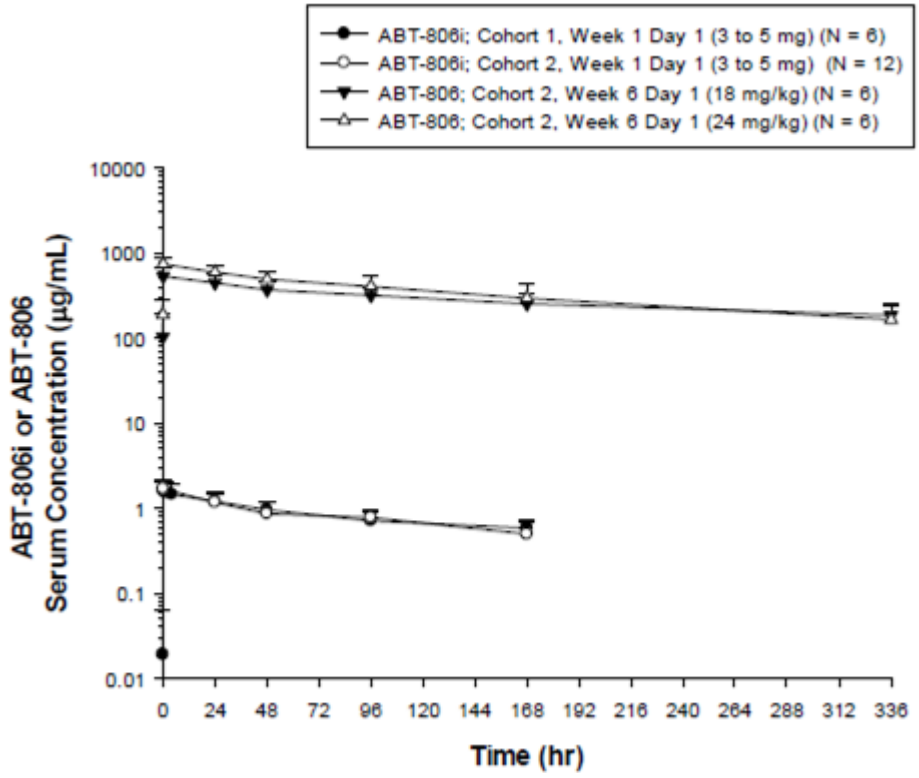


**Figure 3. Serum concentration-time profiles of ABT-806i (Week 1, Day 1) or ABT-806 (Week 6, Day 1) following IV administration.** Mean + standard deviation (SD) is shown on a log-linear scale.

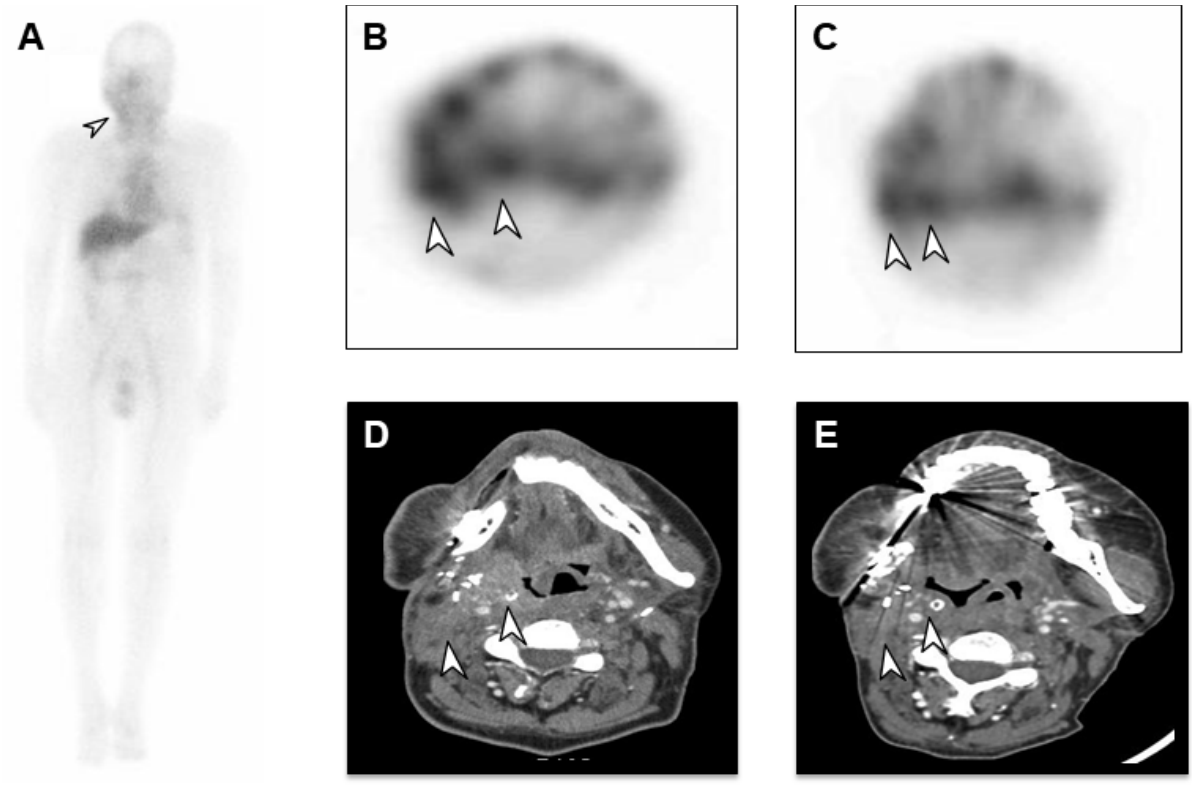


**Figure 4. ABT-806i biodistribution and SPECT/CT images of a patient with squamous cell carcinoma of the head and neck.** (**A**) Whole body planar image of $^{111}$In-ABT-806i biodistribution at day 8 in patient 8. Arrow shows localization in tumor area in the right neck. (**B**) Week 1 SPECT image of $^{111}$In-ABT-806i uptake in right parapharyngeal lesion and right cervical node (arrows), with uptake increased compared to normal tissue. (**C**) Week 16 SPECT image of $^{111}$In-ABT-806i uptake in right parapharyngeal lesion and right cervical node (arrows), which appear smaller than week 1 images. (**D**) CT at baseline showing tumor in the right parapharyngeal region and right cervical node (arrows), which also showed $^{111}$In-ABT-806i uptake. (**E**) CT at week 16 restaging, showing reduction in size of right parapharyngeal lesion and right cervical node (arrows), assessed as RECIST partial response.

**Table 1. Patient demographics.**

| **Characteristics, N (%)** | | **All patients N=18** |
|---|---|---|
| Gender | Male:Female | 11:7 |
| Age (years) | Median | 57 |
| | Range | 37-75 |
| Ethnicity | Caucasian | 17 (92) |
| | Asian | 1 (8) |
| Tumor type | Head and neck | 6 (33) |
| | Colorectal | 3 (17) |
| | Non-small cell lung cancer | 2 (11) |
| | Glioma | 2 (11) |
| | Other* | 5 (28) |
| ECOG performance status | 0 | 5 (28) |
| | 1 | 13 (72) |

*Includes adrenal, cervical, cholangiocarcinoma, transitional cell carcinoma of bladder, thymoma

ECOG, Eastern Cooperative Oncology Group.

**Table 2. Individual patient data.**

| Patient | Cohort | Cancer type | EGFR H-score | Best response on M11-849 study | Best response on M12-326 study |
|---|---|---|---|---|---|
| 1 | 1 | Colon | 0 | Clinically stable | PD |
| 2 | 1 | NSCLC | 3 | Clinically Stable | PD |
| 3 | 1 | HGG | 50 | Clinically Stable | PD |
| 4 | 1 | H&N | 12 | Clinically Stable | PD |
| 5 | 1 | HGG | 295 | Clinically Stable | PD |
| 6 | 1 | Adrenal | 0 | Clinically Stable | SD |
| 7 | 2 | H&N | 80 | PD | N/A* |
| 8 | 2 | H&N | 235 | SD | PR |
| 9 | 2 | Thymoma | 115 | PD | N/A* |
| 10 | 2 | Cholangio-carcinoma | 55 | PD | N/A* |
| 11 | 2 | NSCLC | 278 | SD | PD |
| 12 | 2 | Colon | 0 | SD | PD |
| 13 | 2 | H&N | 170 | SD | PD |
| 14 | 2 | Cervical | 13 | PD | N/A* |
| 15 | 2 | Bladder | 228 | PD | N/A* |
| 16 | 2 | H&N | 67 | PD | N/A* |
| 17 | 2 | Colon | 0 | SD | PD |
| 18 | 2 | H&N | 32 | PD | N/A* |

NSCLC, non-small cell lung cancer; HGG, high grade glioma; H&N, head and neck; N/A Not applicable; PD, progressive disease; SD, stable disease; PR, partial response.

* Patients who had progressive disease at the end of M11-849 study were not eligible for enrolment on the M12-326 extension study

**Table 3. Peak uptake of $^{111}$In-ABT-806i in target tumor lesion in Cohort 1 patients, calculated from SPECT Images**

| | | Ist Infusion $^{111}$In-ABT-806i |
|---|---|---|
| **Subject** | **Site of reference lesion** | **Tumor maximal uptake (%ID)** |
| 1 | left lung | 0.023% |
| 2 | right lung | 0.035% |
| 3 | cerebellum | N/A |
| 4 | left neck | 0.029% |
| 5 | left frontal lobe | N/A |
| 6 | left adrenal | 0.016% |

N/A - no CT data available

**Table 4. Peak uptake of $^{111}$In-ABT-806i in target tumor lesion in Cohort 2 patients, calculated from SPECT/CT Images**

| | | **Ist Infusion $^{111}$In-ABT-806i** | **2nd Infusion $^{111}$In-ABT-806i** |
|---|---|---|---|
| **Subject** | **Site of reference lesion** | **Tumor maximal uptake (%ID)** | **Tumor maximal uptake (%ID)** |
| 7 | right hilum | 1.290% | 1.321% |
| 8 | right pharyngeal | 0.078% | 0.092% |
| 9 | left lung | 0.043% | 0.041% |
| 10 | right peritoneum | 0.265% | 0.264% |
| 11 | subcarinal node | N/A | N/A |
| 12 | right lung | 0.038% | 0.037% |
| 13 | hypopharynx | 0.030% | 0.024% |
| 14 | right hilum | 0.067% | 0.057% |
| 15 | right lung | 0.064% | 0.087% |
| 16 | left lung | 0.050% | 0.051% |
| 17 | right lung | 5.837% | 6.679% |
| 18 | left lung | 0.009% | 0.009% |

N/A - target lesion not assessable for quantitative dosimetry

## Table 5. Pharmacokinetic parameters of ABT-806i and ABT-806

| Cohort (ABT-806 Dose Group) | ABT-806i (mg) | ABT-806 (mg/kg) | N | $T_{max}$ (hr) | $C_{max}$ (µg/ml) | $C_{max}$/Dose (µg/ml)/(mg/kg) | $T_{1/2}$ (days)* | AUC (mg*h/ml)† | AUC/dose (mg*h/ml)/(mg/kg) † | CL (ml/h) |
|---|---|---|---|---|---|---|---|---|---|---|
| ABT-806i (Week 1, Day 1) | | | | | | | | | | |
| 1 | 3-5 | N/A | 6 | 0.41±0.46 | 1.61±0.50 | 23.4±5.2 | 6.0±1.5 | 0.274±0.080 | 4.07±1.10 | 19.4±6.6 |
| 2 (18mg/kg) | 3-5 | N/A | 6 | 0.11±0.04 | 1.62±0.32 | 22.2±4.7 | 5.6±1.5 | 0.243±0.062 | 3.36±1.03 | 21.3±6.1 |
| 2 (24 mg/kg) | 3-5 | N/A | 6 | 0.15±0.10 | 1.75±0.39 | 22.7±5.4 | 5.3±2.4 | 0.261±0.113 | 3.49±1.90 | 24.5±15.9 |
| 2 (18 and 24 mg/kg) | 3-5 | N/A | 12 | 0.13±0.08 | 1.69±0.35 | 22.4±4.8 | 5.4±1.9 | 0.252±0.088 | 3.42±1.46 | 22.9±11.6 |
| ABT-806 + ABT-806i ( Week 6, Day 1) | | | | | | | | | | |
| 2 (18 mg/kg) | 3-5 | N/A | 6 | 2.25±0.49 | 531±136 | 29.5±7.6 | 14.5±4.3 | 99.8±27.9 | 5.54+1.55 | 13.3±4.6 |
| 2 (24 mg/kg) | 3-5 | N/A | 6 | 2.16±0.61 | 742±128 | 30.9±5.3 | 8.6±2.3 | 116.2±38.6 | 4.84±1.61 | 14.8±5.1 |

$T_{max}$ time to maximum concentration in serum; $C_{max}$ maximum observed plasma concentration; $t_{1/2}$ terminal elimination half-life; AUC area under the curve; CL clearance; N/A not applicable.

* Harmonic mean and pseudo-standard deviation

† $AUC_{\infty}$ for Week 1, Day 1 and $AUC_{TAU}$ for Week 6, Day 1

**Supplementary Table 1. Mean organ effective dose (ED) in mSv/MBq for all patients in Cohort 1.**

| Organ | Female (n=4) | | Male (n=2) | |
|---|---|---|---|---|
| | Mean ED (mSv/MBq) | SD | Mean ED (mSv/MBq) | SD |
| Adrenals | 0.0008 | 0.0005 | 0.0005 | 0.0002 |
| Bladder | 0.0103 | 0.0064 | 0.0145 | 0.0048 |
| Brain | 0.0002 | 0.0001 | 0.0002 | 0.0001 |
| Breast | 0.0032 | 0.0018 | 0.0026 | 0.0001 |
| Gall bladder | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Heart | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| Kidney | 0.0018 | 0.0010 | 0.0077 | 0.0092 |
| Large bowel (upper) | 0.0007 | 0.0004 | 0.0004 | 0.0002 |
| Large bowel (lower) | 0.0102 | 0.0059 | 0.0105 | 0.0018 |
| Liver | 0.0261 | 0.0152 | 0.0167 | 0.0052 |
| Lungs | 0.0264 | 0.0165 | 0.0201 | 0.0010 |
| Muscle | 0.0003 | 0.0002 | 0.0002 | 0.0001 |
| Osteogenic cells | 0.0015 | 0.0009 | 0.0014 | 0.0002 |
| Ovaries | 0.0195 | 0.0111 | - | - |
| Pancreas | 0.0008 | 0.0005 | 0.0005 | 0.0002 |
| Red marrow | 0.0121 | 0.0068 | 0.0134 | 0.0012 |
| Skin | 0.0004 | 0.0002 | 0.0003 | 0.0001 |
| Small bowel | 0.0010 | 0.0005 | 0.0006 | 0.0002 |
| Spleen | 0.0014 | 0.0009 | 0.0011 | 0.0002 |
| Stomach | 0.0233 | 0.0134 | 0.0184 | 0.0028 |
| Testes | - | - | 0.0000 | 0.0000 |
| Thymus | 0.0005 | 0.0003 | 0.0003 | 0.0001 |
| Thyroid | 0.0052 | 0.0030 | 0.0073 | 0.0004 |
| Uterus | 0.0005 | 0.0003 | - | - |
| MEAN ± SD | 0.183 | 0.021 | 0.137 | 0.008 |

SD, standard deviation