Investigator's Brochure

for

[18F] 4-L-Glutamine (2S,4R)

AN INVESTIGATIONAL POSITRON EMISSION TOMOGRAPHY (PET) RADIOPHARMACEUTICAL

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1. SUMMARY

[^{18}F] 4-L-Glutamine (2S,4R) is an investigational radioactive imaging agent, for positron emission tomography (PET), developed by the Thompson Laboratory. [18F] 4-L-Glutamine (2S,4R) has a molecular structure similar to L-glutamine, with a positron-emitting 18F atom in place of a hydrogen atom.

2. INTRODUCTION

Fluorine 18 (^{18}F) 4-fluoro-glutamine (2S,4R) (FGln) is an investigational noninvasive positron emission tomography (PET) biomarker assay of in vivo tumor glutamine flux and metabolism. [18F] 4-L-Glutamine (2S,4R) demonstrates uptake in cancer cells similar to FDG, with cellular uptake of [Fl 4-L-Glutamine (2S,4R) mediated by native L-glutamine transporters.

The amino acid glutamine is key in the metabolism of proliferating cells. Cancer cells modify the consumption and processing of glutamine to sustain cell growth and proliferation and can become addicted to glutamine. Thus, targeting the metabolism of glutamine has been recently explored as a potential strategy against cancer.

Glutamine is the most abundant free amino acid in the blood, whose circulating concentration is around 0.5 mmol/L. Despite being a nonessential amino acid, glutamine is physiologically an essential source of carbon and nitrogen for cancer cell proliferation (Brosnan et al. 2003). Glutamine uptake is increased specifically in cancer cells that have dysregulated oncogenes and tumor suppressors, such as c-myc.

Glutamine occupies a unique niche in intermediary metabolism by providing a major inter-organ shuttle for both nitrogen and carbon. Recent work has demonstrated that aspects of glutamine metabolism are under the control of oncogenes and tumor suppressors. Glutamine contributes to essentially every core metabolic task of proliferating tumor cells: it participates in bioenergetics, supports cell defenses against oxidative stress and complements glucose metabolism in the production of macromolecules. The interest in glutamine metabolism has been heightened further by the recent findings that c-myc controls glutamine uptake and degradation, and that glutamine itself exerts influence over a number of signaling pathways that contribute to tumor growth. Some cancer cells produce more than 50% of their adenosine; triphosphate (ATP) fuel supply by oxidizing glutamine derived α- ketoglutarate in the mitochondria.

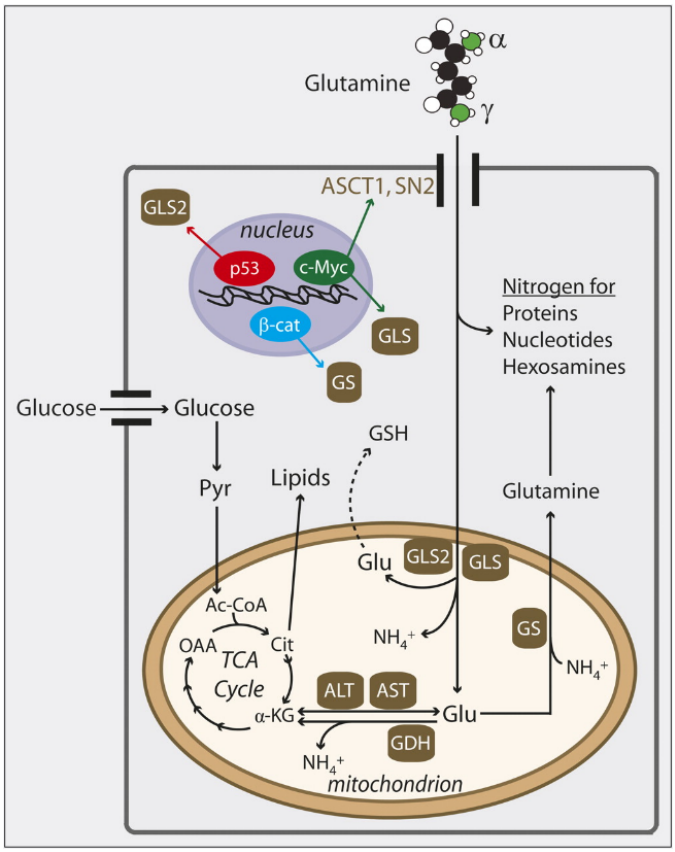


Figure 1. Glutamine metabolism in cancer cells and its regulation by oncogenes and tumor suppressors (Rajagopalan and DeBerardinis et al. 2011).

After glutamine is imported into the cell through surface transporters such as ASCTI or SN2, most of it either donates nitrogen to macromolecules or is deamidated by glutaminases, which remove γ-nitrogen to form glutamate (Glu). Glu can be used for biosynthesis of glutathione (GSH) or processed further in mitochondria, where removal of α-nitrogen by aminotransferases or glutamate dehydrogenase (GDH) produces α-ketoglutarate (α-KG). Because many of the metabolic functions supplied by glutamine are independent of those supplied by glucose, imaging glutamine metabolism would provide a window into aspects of tumor biology different from those shown by FDG PET, It is also possible that these agents would be useful in patients subjected to drugs that suppress glucose uptake, such as inhibitors of the signaling pathway phosphatidylinositol-3' kinase/protein kinase B (Akt)/mammalian target of rapamycin since in culture, cells exposed to these agents require ongoing glutamine use to maintain survival when glucose metabolism is compromised.(Yang, Sudderth et al. 2009).

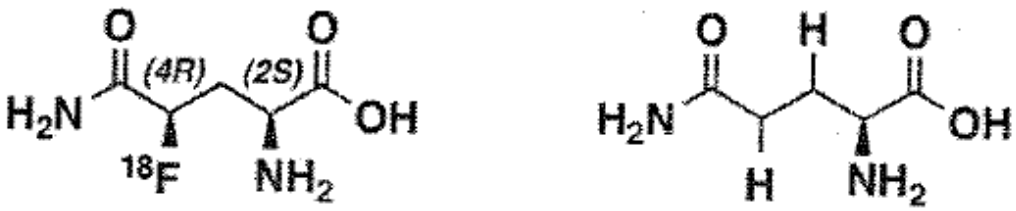
3. [18F] 4-L-GLUTAMINE (2S,4R) PRODUCT AGENT DESCRIPTION

3.1. Agent Description

[18F] 4-L-Glutamine (2S,4R) is an investigational radioactive imaging agent, for positron emission tomography (PET), developed by the Thompson Laboratory. (1,2) 18F] 4-L-Glutamine (2S,4R) has a molecular structure similar to L-glutamine, with a positron-emitting 18F atom in place of a hydrogen atom.

3.2. Chemical Structure

Figure 2. Molecular structures of [18F] 4-L-Glutamine (2S,4R) (Left) and glutamine.



[^{18}F] 4-L-Glutamine (2S,4R) *Glutamine*

1 Lieberman BP, Ploessl K, Wang L, Qu W, Zha Z, Wise DR, Chodosh LA, Belka G, Thompson CB, Kung HF. PET imaging of glutaminolysis in tumors by 18F-(2s,4r)4-fluoroglutamine. *Journal of Nuclear Medicine.* 2011;52:1947-1955

2 Qu W, Zha Z, Ploessl K, Lieberman BP, Zhu L, Wise DR, Thompson CB, Kung HF. Synthesis of optically pure 4-fluoro-glutamines as potential metabolic imaging agents for tumors. J Am Chem Soc. 2011;133:1122-1133

3.3. Final Product Specifications

Table 1. Specifications for [18F] 4-L-Glutamine (2S,4R) solution

PRE-RELEASE TEST	DESCRIPTION	REQUIREMENTS FOR PASS
Appearance (particulates)	Visual inspection for color and particulates	**Clear and Colorless**
pH	USP <791> pH strips	**pH must be between 5.0 and 7.5**
Radionuclidic Identity	Half-life determination	**105 – 115 minutes**
Radiochemical Identity	HPLC - Compare retention time with reference standard	**Sample retention time conforms to the reference standard retention time**
Chemical Purity	HPLC	**1) L-Glutamine (2S,4R) mass of less than 100 micrograms per dose** **2) Total UV impurities mass of less than 100 micrograms per dose.**
Radiochemical Purity	HPLC	**Radiochemical Purity > 80%**
Residual Solvent Levels	Gas Chromatography	**Ethanol: <5000 µg/mL** **Acetonitrile < 410 µg/mL** **Methanol <3000 µg/mL**
Filter Integrity	Test bubble point	**Meets pressure specified by manufacturer (>50psi)**
Bacterial Endotoxin Levels	Limulus Amoebocyte Lysate (LAL) by PTS	**< 5 EU/ml**
Radioactive Concentration	Calculation	**Radioactive concentration of NLT 1.2mCi at ToI for a maximum injection volume of 10mL**
POST-RELEASE TEST	**DESCRIPTION**	**REQUIREMENTS FOR PASS**
Sterility	USP sterility test (USP <823>)	**No growth observed in 14 days**

*United States Pharmacopeia (USP)

4. NONCLINICAL STUDIES

4.1. Introduction

Lieberman et al. (2011) studied in vivo biodistribution of [18F] 4-L-Glutamine (2S,4R) in ICR mice; and showed the expected behavior of a radiolabeled amino acid with significant pancreas uptake (19.7% injected dose/g at 30 min), most likely due to the exocrine function and high protein turnover within the pancreas. Blood levels drop quickly with time, showing low blood activity at 240 min after injection (0.48% dose/g). There was no significant uptake within the lung, along with no significant retention within the first arteriovenous capillary bed, suggesting that [18F] 4-L-Glutamine (2S,4R) is hydrophilic and water-soluble. Rapid uptake is observed within the kidneys but is quickly excreted through the urinary bladder. [18F] 4-L-Glutamine (2S,4R) showed a moderate liver uptake with a relatively slow washout rate. Brain uptake exhibited a relatively low, but consistent, uptake of 0.54 %ID/g at 2 min after injection and remained consistent with little to no washout throughout the 240-min experiment. Lastly, bone (femur) showed rapid uptake and increased with time, implying that in vivo defluorination may be occurring after injection.

4.2. Nonclinical Pharmacology

Uptake of [18F] 4-L-Glutamine (2S,4R) in Fischer 344 rats bearing 9L xenografts showed tumor uptake values of 1.03% dose/gram uptake at 30 min post injection: tumor/muscle ratio (target/background) decreased slightly from 2.78 at 30 min to a ratio of 2.00 at 60 min post injection and then stabilized at least up to 120 min. (Lieberman, Ploessl et al. 2011) Results of biodistribution studies also showed a high pancreas uptake, similar to what was found in mice, again due to the various amino acid precursors used for protein and peptide synthesis. Bone uptake (femur) slightly rose from 30 min to 60 min post injection, suggesting in vivo de-fluorination.

4.3. PET imaging studies in F344 rats with 9L xenografts and transgenic mice with M/tomND spontaneous tumors

Animal PET imaging studies using [18FJ 4-L-Glutamine (2S,4R) exhibited the expected high uptake and retention in the tumor models in rats (9L xenografted tumor) and mice (in m/tomND transgenic mice with spontaneous tumors). (Lieberman, Ploessl et al. 2011) Rapid tumor uptake is visualized within each animal model within the first 20 min. Tumor uptake remains rather consistent throughout the 2-hour scan time, with a slow washout rate observed. High kidney and bladder uptake is observed. Clear tumor uptake is visualized in this animal model. In addition, ex-vivo animal PET imaging studies in a transgenic mouse with M/tomND spontaneous tumors were performed after dissection. A clear tumor uptake is also visualized within the m/tomND spontaneous tumor. High

uptake of [18F-4-L-Glutamine (2S,4R) is also apparent in other peripheral organs such as the liver, kidneys, and pancreas regions. This data is consistent with in-vivo imaging studies conducted in 9L rat xenografted animal model.

Table 2. In Vivo Biodistribution of 18F-(2S,4R)4-Fluoroglutamine in Male ICR Mice After Intravenous Injection

Organ	2 min	30 min	60 min	120 min	240 min
Blood	6.19 ± 0.83	2.72 ± 0.17	2.05 ± 0.16	0.83 ± 0.12	0.48 ± 0.06
Heart	4.31 ± 0.32	3.16 ± 0.25	2.86 ± 0.47	1.96 ± 0.24	1.24 ± 0.19
Muscle	1.62 ± 0.10	2.48 ± 0.16	2.86 ± 0.34	1.81 ± 0.26	0.94 ± 0.15
Lung	7.15 ± 0.76	5.36 ± 0.49	4.37 ± 0.28	1.69 ± 0.10	1.03 ± 0.15
Kidney	16.1 ± 1.03	9.93 ± 0.52	7.60 ± 0.84	2.15 ± 0.34	1.25 ± 0.21
Pancreas	17.2 ± 1.00	19.7 ± 2.16	17.5 ± 2.28	9.57 ± 1.22	5.92 ± 0.87
Spleen	7.51 ± 0.44	5.39 ± 0.72	4.22 ± 0.38	2.02 ± 0.16	1.15 ± 0.14
Liver	6.92 ± 0.92	6.23 ± 0.50	5.70 ± 0.62	2.46 ± 0.26	1.30 ± 0.18
Skin	2.72 ± 0.05	4.01 ± 0.24	2.94 ± 0.68	2.17 ± 0.16	1.25 ± 0.13
Brain	0.54 ± 0.05	0.51 ± 0.05	0.53 ± 0.07	0.5 ±0.05	0.45 ± 0.06
Bone	3.93 ± 0.37	5.64 ± 0.89	7.93 ± 1.02	14.4 ± 1.31	19.4 ± 0.50

* *Data represented as% dose/gram, mean± S.D. (five mice per time point).*

4.4. Pharmacokinetics and Product Metabolism in Animals

Metabolism Studies: In vivo metabolism studies in transgenic mice with m/tomND spontaneous tumors and F344 rats bearing 9L tumor xenografts

Metabolites of [18F] 4-L-Glutamine (2S,4R) were measured in tumor cells 30 min after injection into transgenic mice with m/tomND spontaneous tumors and F344 rats bearing 9L tumor models.(1) Tumors were homogenized, centrifuged, and separated into a pellet and supernatant. The results suggest that a significant amount of injected [18F] 4-L-Glutamine (2S,4R) is retained in tumors either by incorporation into protein synthesis or by metabolism to [18F] (2S,4R)4-fluoro-glutamic acid. This mechanism can be advantageous to retention of the PET tracer in cells. In animal biodistribution studies, a prominent, progressive accumulation of F-18 tracer was observed in the skeleton across sampling time-points (Tables 2 and 3). This osseous tracer-accumulation might represent accumulation of free fluorine-18 produced by in vivo metabolism/defluorination of the [18F] 4-L-Fluoroglutamine (2S,4R). As table 4 indicates, the majority off-18 tracer in soft tissue tumors, in animal models, was intact [18FJ 4-L-Fluoroglutamine (2S,4R).

Table 3. Metabolite analysis in spontaneous tumors of transgenic mice and 9L tumors of F344 rats after an iv injection of [^{18}F] 4-L-Glutamine (2S,4R) at 1 hour post injection.

Animal	Percentage parent [I F) 4-L-Fluoroglutamine (2S,4R)	Percentage metabolized *^{18}F-(2S,4R)* 4-fluoro-glutamic acid	Percentage protein pellet activity
Transgenic mice (n= 3)	79 ± 6.0	8.0± 3.0	29 ± 6.0
F344 rats *(n*=2)	76 ±2.0	9.0± 1.0	37±20

4.5. Toxicology

4.5.1. Summary of Single Dose Toxicity in B6D2F1 mice[3]

An acute toxicology study at 0.2 and 2 mg/kg (corresponding to 120 and 1200 times respectively of the maximum anticipated dose required for clinical imaging (hot-only, less than 100 micrograms) calculated with a HED based on body surface area: 162 mg/kg, human weight: 60 kg; mouse weight: 20 g) and with a 14-day recovery period, was conducted in 8-week-old B6D2FI mice. All animals survived to scheduled necropsies and there were no remarkable clinical observations, clinical pathology, or anatomic pathology in males or in females at primary or recovery necropsy that were attributed to the test article.

4.5.2 Details of Single Dose Toxicity in B6D2F1 mice study

The purpose of this study was to determine the general systemic safety of 4-L-Fluoroglutamine (2S,4R) in mice, at a high multiple of the anticipated clinical microdose in humans. 4-L- Fluoroglutamine (2S,4R) was administered to B6D2F1 mice intravenously as a single dose of 0.2 or 2 mg/kg. This is equivalent to 120 or 1200 times (based on body surface area) the single dose tracer amount of [18F] 4-L-Fluoroglutamine (2S,4R), that was used in first-in-human study. Animals were monitored for two-weeks after dosing, clinical chemistries and hematology were drawn at day 2 and day 14 and a primary (at day 2) and secondary (at day 14) necropsy were performed. Clinical signs, mortality, morbidity, and clinical pathology were recorded for all animals, including control (vehicle only) groups.

8 week old B6D2F1 mice were randomly assigned to either control or treatment groups and each group received one single dose of test article through an intravenous injection once. Toxicity was monitored by weight loss and daily clinical observation for the 14 days following test article administration. 24 hrs after test article administration 20 mice (10 males+ 10 females) in each group were sacrificed and clinical chemistry, hematology and tissue specific histopathology were done at

3 GLP toxicology study performed by Memorial Sloan Kettering and filed in their original IND

autopsy. The remaining mice (n = 5 males+ 5 females/group) were kept under observation for an additional 13 days; at that point all mice were sacrificed, and clinical chemistry and hematology were done at time of autopsy. Four untreated mice (two males and two females} were used as reference.

No unacceptable adverse events were related to the test article during acute dosing or the following 14-day observation periods. There were no clinical signs or changes in body weights that could be attributed to treatment and no macroscopic findings. None of these effects correlated with histopathological lesions or interfered with animal well-being. This study established 2 mg/kg to represent the No Observed Adverse Effect Level (NOAEL) for (2S, 4R)-4-Fluoro-L-Glutamine administered i.v in B6D2Fl mice. Cold 4-L-Fluoroglutamine (2S,4R) was prepared in the intended clinical formulation (0.9% NaCl solution in water, for injection, USP) and the characteristics and acceptance criteria for the product was equivalent to those of the product intended for clinical use. Table 4 below summarizes of the study conducted at MSKCC.

Table 4. Summary of Mouse Toxicology Study

Species	Mice, 8 wks
Strain	B6D2Fl
Supplier	Jackson Laboratories
# **Animals**	64 (32 male+ 32 female)
Study Design	Single i.v.-injected dose (0, 0.2 and 2 mg/kg) of non-radiolabeled test probe was administered followed by a 14-day observation period. 30 vehicle control animals (1% serum albumin), 30 treated (Fluoroglutamine), and 4 untreated mice were studied. Full chemistry, hematology, gross necropsy, and histopathology were performed.
Test Article	4-1-Fluoroglutamine (2S,4R)
Conducting laboratory	Anti-tumor Assessment Core• MSKCC

5. EFFECTS IN HUMANS

5.1. Pharmacokinetics and Product Metabolism in Humans

Pharmacokinetic study. (4) Fifty lesions from 41 patients (21M/20F, aged 54±14 years) were analyzed. 30-min dynamic PET scans were performed concurrent with a rapid intravenous bolus injection of 232±82 MBq of 18F-FGln, followed by two static PET scans at 97±14 min and 190±12 min post-injection. Five patients also underwent a second 18F-FGln study 4-13 weeks after initiation of therapy with either glutaminase, dual TORC1/2, or PD-1 inhibitors. Blood samples were collected to determine plasma and metabolite fractions and to scale the image-derived input function. Regions of interest were manually drawn to calculate standardized uptake values (SUVs). Pharmacokinetic modeling with both reversible and irreversible one- and two-tissue compartment models was performed to calculate kinetic rate constants K1, k2, k3, and k4. The analysis was repeated with truncated 30-min dynamic datasets.

Intratumor 18F-FGln uptake patterns demonstrated substantial heterogeneity in different lesion types. In majority of lesions, reversible two-tissue compartment model was chosen as the most appropriate according to the Akaike Information Criterion. K1, a surrogate biomarker for 18F-FGln intracellular transport, was the kinetic rate constant that was most correlated with both SUV at 30-min (Spearman's ρ=0.71) and with SUV at 190-min (ρ=0.51). Only K1 was reproducible from truncated 30-min datasets (ICC=0.96). k3, a surrogate biomarker for glutaminolysis rate, was relatively low in ~50% of lesions. Treatment with glutaminase inhibitor CB-839 substantially reduced the glutaminolysis rates as measured by k3.

4 Grkovski M, Goel R, Krebs S, Staton KD, Harding JJ, Mellinghoff IK, Humm JL, Dunphy MP. Pharmacokinetic assessment of ^{18}F-(2S,4R)-4-fluoroglutamine in patients with cancer.J Nucl Med. 2019 Oct 10. pii: jnumed.119.229740. doi: 10.2967/jnumed.119.229740.

5.2. Human Studies

Table 6. Published manuscripts reporting [18F] 4-L-Glutamine (2S,4R) human imaging

Clinical Condition	No. of Patients	MBq Injected	mCi injected (mean)	Reference
Various Cancer	31	3.7/kg	0.1	Xu (2020)
Various Cancer	41	232 ± 82	6.3 ± 2.2	Grkovski (2020)
Brain	1	3.7/kg	0.1	Zhang (2019)
Various Cancer	25	244 ± 118	6.6±3.2	Dunphy (2018)
Brain	14	3.7/kg	0.1	Xu (2018)
Total No. Subjects:	**112**			

*Although every attempt to eliminate duplication was made, it is possible that some patients are counted twice due to representation in multiple publications.

2. **First in human study.** (5) Six glioma patients were administered a single peripheral intravenous injection of 125 MBq as a slow bolus (1-min duration) in a volume of 5 to 10 ml. Imaging of 18F-FGln biodistribution was obtained at about 30, 90, and 160 min after injection. They compared 18F-FGln uptake in three glioma patients with clinical progression of disease and three patients with stable disease. Normal brain parenchyma showed minimal 18F-FGln uptake, and 18F-FGln avidity was noted in all tumors that showed progression within the three patients. In contrast, clinically stable tumors showed minimal or no 18F-FGln avidity on PET.
3. **Exploratory Phase I study.** (6) Twenty-five adult patients with cancer received an intravenous bolus of FGln tracer (mean, 244 MBq ± 118, <100 µg) followed by positron emission tomography (PET) and blood radioassays. FGln PET depicted tumors of different cancer types (breast, pancreas, renal, neuroendocrine, lung, colon, lymphoma, bile duct, or glioma) in 17 of the 25 patients, predominantly clinically aggressive tumors with genetic mutations implicated in abnormal glutamine metabolism. Acute fasting had no significant effect on FGln

5 Venneti S, Dunphy MP, Zhang H, Pitter KL, Zanzonico P, Campos C, Carlin SD, La Rocca G, Lyashchenko S, Ploessl K, Rohle D, Omuro AM, Cross JR, Brennan CW, Weber WA, Holland EC, Mellinghoff IK, Kung HF, Lewis JS, Thompson CB. Glutamine-based PET imaging facilitates enhanced metabolic evaluation of gliomas in vivo. Sci Transl Med. 2015 Feb 11;7(274):274ra17. doi: 10.1126/scitranslmed.aaa1009

6 Dunphy M.P.S., Harding J.J., Venneti S., Zhang H., Burnazi E.M., Bromberg J., Omuro A.M., Hsieh J.J., Mellinghoff I.K., Staton K., Pressl C., Beattie B.J., Zanzonico P.B., Gerecitano J.F., Kelsen D.P., Weber W., Lyashchenko S.K., Kung H.F., Lewis J.S. In vivo PET assay of tumor glutamine flux and metabolism: In-human trial of ^{18}f-(2S,4R)-4-fluoroglutamine, Radiology 2018 287:2 (667-675)

biodistribution and plasma amino acid levels. FGln-avid tumors were uniformly FDG-avid but not vice versa (P = .07). Patients experienced no adverse effects.

4. **A Phase I study.** (7) PET/CT imaging of 18F-FGln was compared with 18F-FDG in the same group of breast cancer patients (n = 10). In this preliminary clinical study, 18F-FGln/PET detected more lesions in breast cancer patients than 18F-FDG/PET (90%vs 80%).
5. **A phase I study.** (8) Patients (7 men and 7 women; age, 25-67 years) with suspected brain metastasis were enrolled for this study. All patients were imaged first with 3.7 MBq/kg ^{18}F-FGln PET (3 patients for 1-hour dynamic whole-body PET/CT scans, and 11 patients for static whole-body scans at 30 ± 10 minutes after injection), followed by a whole-body ^{18}F-FDG PET performed in the same week. The characteristics of ^{18}F-FGln PET imaging in brain metastasis patients were compared with that of ^{18}F-FDG PET and/or contrast-enhanced MRI patient-by-patient. A composite of all functional and anatomic imaging studies served as the imaging comparator. **Results** Initial study in 3 patients using 1-hour dynamic scan showed that 30 ± 10 minutes after injection is optimal for identifying brain metastasis with a high-contrast ratio. All patients were positive for brain metastasis on this study that demonstrated 38 lesions in 6 anatomic regions on the imaging comparator. The per-lesion detection rates for ^{18}F-FGln PET and ^{18}F-FDG PET were 81.6% and 36.8%, respectively. The average tumor-to-normal brain ratio of ^{18}F-FGln PET was significantly better than that of ^{18}F-FDG PET in all patients (4.97 ± 2.23 vs 1.22 ± 0.69, P < 0.05). Furthermore, the results suggest that ^{18}F-FGln uptake in brain metastasis appeared to be independent of tumor size and peripheral edema. In addition, in 14 brain metastatic lesions visualized by both ^{18}F-FDG PET and ^{18}F-FGln PET imaging, a positive correlation of SUV_{max} was observed (r = 0.780, P < 0.01). As to the extracranial metastasis, both tracers showed a concordant increased radioactive uptake except in liver and bone.
6. **Abstracts.** Several abstracts have been presented at meetings by the two groups active in this area, Memorial Sloan Kettering group and the Beijing group. They are not included as they have not been peer-reviewed.

5.3 Human Toxicity

No adverse events have been reported related to the FGln injection in any of the trials.

7 Liu F., Xu X., Zhu H., Zhang Y., Yang J., Zhang L., Li N., Zhu L., Kung H.F., Yang Z. PET Imaging of ^{18}F-(2 S,4 R)4-Fluoroglutamine Accumulation in Breast Cancer: From Xenografts to Patients Molecular Pharmaceutics 2018 15:8 (3448-3455)

8 Xu X., Zhu H., Liu F., Zhang Y., Yang J., Zhang L., Zhu L., Li N., Kung H.F., Yang Z. Imaging Brain Metastasis Patients with 18F-(2S,4 R)-4-Fluoroglutamine, Clinical Nuclear Medicine 2018 43:11 (e392-e399)

5.4. Dosimetry

The table, below, provides ^{18}F-glutamine human dosimetry estimates for the organs receiving the highest dose (Venneti et al. 2015).

Table 5. Human Dosimetry Estimates for Organs Receiving Highest dose

Organ	Average (rem/mCi)	Stdev
Adrenals	0.03	0.01
Brain	0.02	0.00
Breasts	0.01	0.00
Gallbladder wall	0.04	0.01
Lower large Intestine wall	0.07	0.02
Small intestine	0.13	0.04
Stomach wall	0.02	0.01
Upper large Intestine wall	0.14	0.05
Heart wall	0.05	0.02
Kidneys	0.06	0.02
Liver	0.08	0.01
Lungs	0.02	0.01
Muscle	0.04	0.01
Ovaries	0.05	0.02
Pancreas	0.09	0.01
Red marrow	0.07	0.02
Osteogenic cells	0.08	0.03
Skin	0.01	0.00
Spleen	0.05	0.02
Testes	0.02	0.01
Thymus	0.02	0.01
Thyroid	0.02	0.01
Urinary bladder wall	0.69	0.36
Uterus	0.06	0.03
Total body	0.03	0.01
Effective dose	0.07	0.02

18F-FGln radiation dosimetry in human subjects, including organ absorbed doses (rem/mCi) and effective dose (rem/mCi). For each organ, the time-activity data from the human PET-based biodistribution studies of 18F-FGln were fit to an exponential function using least-squares regression (Excel, Microsoft Corp). The fitted time-activity concentration functions were analytically integrated (incorporating the effect of the

physical decay of 18F) and converted from concentrations to total organ values using the 70-kg Standard Man organ masses to yield the respective organ residence times (h) (30). The rest-of-body residence time was calculated as the difference between the total-body residence time and the sum of the normal-organ residence times. The red marrow cumulative activity was estimated from the blood residence time, assuming instantaneous equilibration of the 18F activity between plasma and marrow extracellular space, a plasmacrit of 0.6, and a marrow fractional extracellular space of 0.4. Finally, the mean normal-organ radiation doses (cGy/MBq 18F-FGln administered) and the effective dose (cSv/MBq [18F]-fluoroglutamine administered) were calculated for the 70-kg Standard Man anatomic model with scaling of the organ masses to those of the respective patient's total-body mass using the "MIRD formalism", as implemented in the OLINDA EXM program.

6. Marketing Experience

To the best of our knowledge, this drug has not been marketed anywhere.

7. Summary of Data and Guidance for the Investigator

56 patients have received 18F-FGln to date. No adverse effects have been reported. Investigators are required to monitor patients for adverse events for 10 half-lives, or approximately 24 hours after administration of the agent.

8. REFERENCES

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3. Venneti S, Dunphy MP, Zhang H, et al. Glutamine-based PET imaging facilitates enhanced metabolic evaluation of gliomas in vivo. Sci Transl Med. 2015 Feb 11;7(274):274ra17. doi: 10.1126/scitranslmed.aaa1009.

4. Dunphy M, Harding J, Venneti S, et al. In vivo PET assay of tumor glutamine flux and metabolism: In-human trial of 18f-(2S,4R)-4-fluoroglutamine, Radiology 2018 287:2 (667-675).

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