Iodine-124-Evuzamitide PET/CT in Systemic Amyloidosis: Safety Evaluation & Reproducibility of Cardiac Uptake Quantitation

216-04

Gregory Bell,[1] Claire Sherman,[1] Akari Yamagami,[1] I-Ling Hsuie,[1] Dustin C. Powell,[2] Ming Yang,[3] Matthew D. L. Kay,[4] Deepak Behera,[5] Matthew F. Covington,[6] Don C. Yoo,[7] Phillip H. Kuo[8]

[1]Attralus, Inc., San Francisco, CA, USA; [2]Hendersonville Radiological Consultants, Hendersonville, NC, USA; [3]Mayo Clinic-Phoenix, Phoenix, AZ, USA; [4]Tualatin Imaging, PC, Tualatin, OR, USA; [5]Medical Imaging Consultancy, San Carlos, CA, USA; [6]University of Utah, Salt Lake City, UT, USA; [7]Warren Alpert Medical School of Brown University, Providence, RI, USA; [8]University of Arizona, Tucson, AZ, USA

Background

- Systemic amyloidosis is a rare protein misfolding and deposition disorder that results in progressive tissue amyloid accumulation and organ dysfunction[1,2]
- This heterogeneous disease can be acquired or hereditary and encompasses several subtypes, including AL amyloidosis and ATTR amyloidosis, each driven by distinct amyloidogenic proteins[1,2]
- Systemic amyloidosis is an incurable disease, and patients diagnosed at advanced stages, particularly when cardiac involvement is present, are at high risk of death within a few months[3,4]
- Cardiac involvement in systemic amyloidosis manifests as heart failure with preserved ejection fraction, causing exertional dyspnea, fluid retention, and hypotension[2,5]
- Accurate and timely diagnosis of systemic amyloidosis with cardiac involvement is critical to improve prognosis of these patients[1]
- Although PET/CT has been shown to be a promising imaging modality for amyloid deposits in the brain, there are no approved PET tracers that specifically detect and quantify cardiac amyloid deposits[1,6]
- PET/CT imaging with ^{124}I-evuzamitide, an amyloid-reactive synthetic peptide radiolabeled with ^{124}I, has potential to improve the diagnosis and management of systemic amyloidosis

Objectives

- To evaluate the repeatability of cardiac quantitation of radiotracer uptake following PET/CT imaging of ^{124}I-evuzamitide in subjects with AL or ATTR systemic amyloidosis
- To characterize the safety and tolerability of repeat doses of ^{124}I-evuzamitide administered by IV infusion or slow IV bolus

Methods

Study Design

- This multicenter, open-label, single-arm study in subjects with AL or ATTR systemic amyloidosis comprised a 30-day screening period, two 1-day dosing periods (Day 1 and Week 6 Visits), and safety follow-ups 1 to 3 days and 28±3 days after the second administration of ^{124}I-evuzamitide
- At Visits 1 and 2, subjects received 1 mCi (≤2 mg peptide) ^{124}I-evuzamitide by IV infusion over 2 to 5 minutes or slow IV push
  1 mL/5 seconds
- Subjects were treated with KI 130 mg orally once every day for 3 days beginning at least 30 minutes and within 24 hours prior to each administration of ^{124}I-evuzamitide
- Base of skull to mid-thigh PET/CT imaging was performed 5 hours (± 30 minutes) after ^{124}I-evuzamitide administration
- Subjects were discontinued if amyloid deposits were not identified in the Day 1 PET/CT scan in ≥1 of the following organs: heart, liver, spleen, or kidney

Inclusion Criteria

- Patients aged ≥18 years with a history of AL or ATTR (wild type or variant) systemic amyloidosis with ≥1 organ with clinically demonstrable amyloid involvement
- AL subjects must have achieved CR or VGPR based on their most recent assessment and within 12 months of screening

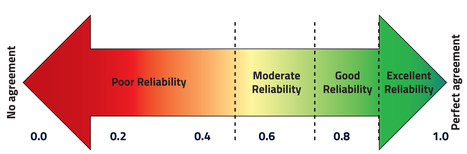
Outcomes and Assessments

- Primary efficacy endpoints included the ICC, RC, and Bland-Altman plots associated with the quantitative ^{124}I-evuzamitide uptake measurements
  - For qualitative assessment, 3 readers scored each scan (twice) as positive or negative for amyloid in the heart on Visit 1 and Visit 2
  - SUV assessments of the heart were performed twice on each scan by 3 independent blinded readers trained by the imaging core lab (Invicro, LLC)
- The incidence of AEs was recorded from Visit 1 through the final safety follow-up/EOS

ICC Guidelines

- ICC was an index to assess reliability and represented a ratio of true variance (between-subject variability) over true variance plus error variance (measurement variability; **Figure 1**).

Figure 1. ICC Guidelines



Results

Subject Characteristics

- 34 subjects were screened, 33 were enrolled and received ≥1 dose of ^{124}I-evuzamitide (SAF), and 27 received 2 doses of ^{124}I-evuzamitide (image-evaluable population)
- Most subjects were male and White with a median age of 66.0 years; 63.6% and 36.4% of subjects had AL and ATTR, respectively (**Table 1**)

Table 1. Demographic and Baseline Characteristics

Characteristic	N=33[a]
Male, n (%)	20 (60.6)
Age, mean (SD), y	65.1 (10.9)
Race, n (%)	
White	30 (90.9)
Black or African American	2 (6.1)
Multiple	1 (3.0)
Ethnicity, n (%)	
Not Hispanic or Latino	32 (97.0)
Not reported	1 (3.0)
BMI, mean (SD), kg/m²	27.9 (5.4)
Time since diagnosis of amyloidosis, mean (SD), y	4.7 (3.2)
Clinical organ involvement (subjects may have amyloidosis in more than 1 organ), n (%)	
Heart	23 (69.7)
Kidney	13 (39.4)
Liver	4 (12.1)
Spleen	0
Amyloid subtype, n (%)	
AL	21 (63.6)
Lambda[b]	12 (57.1)
Kappa[b]	7 (33.3)
Unknown[b]	2 (9.5)
ATTR	12 (36.4)
ATTRwt[c]	5 (41.7)
ATTRv[c]	7 (58.3)
eGFR, mean (SD), mL/min/1.73 m², (N=32)	65.7 (22.3)
NT-proBNP, mean (SD), pg/mL (N=30)	760.2 (1113.6)

[a]Data are presented for the SAF, which included all subjects who received any amount of ^{124}I-evuzamitide.
[b]Denominators for percentages included AL subjects.
[c]Denominators for percentages included ATTR subjects.

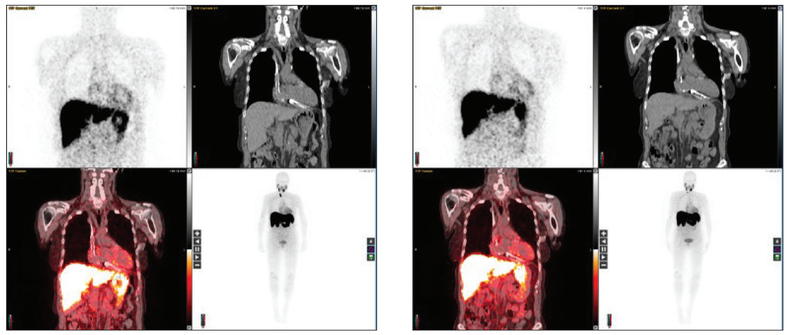
Efficacy Endpoints

ICC estimates for cardiac SUV_{max} and SUV_{peak} indicated excellent intra-reader reliability (**Table 2**)

Table 2. Intraclass Correlation Coefficients for Between-Reader Repeatability for Cardiac SUV_{max} and SUV_{peak}

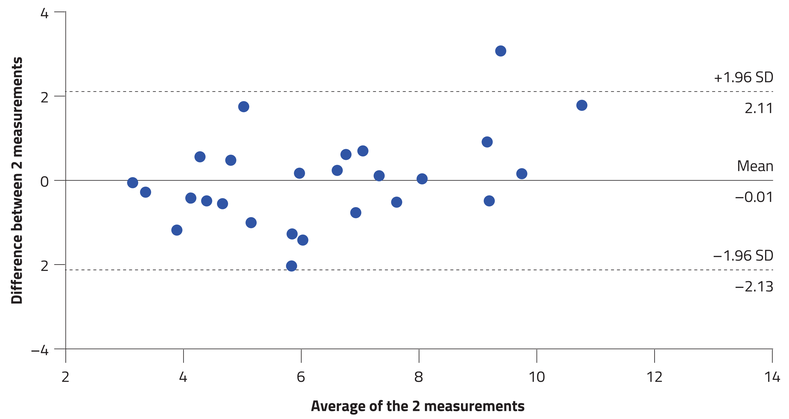
Measure	Visit	ICC (95% CI)
SUV_{max}	1	0.90 (0.80-1.00)
	2	0.96 (0.90-0.98)
SUV_{peak}	1	0.96 (0.91-0.98)
	2	0.99 (0.97-0.99)

Figure 2. PET/CT Scans at Visit 1 and Visit 2



At Visit 1, cardiac SUV_{peak} was 6.4, SUV_{max} was 10.6, and SUV_{mean} was 4.1; at Visit 2, these values were 7.0, 10.6, 4.6, respectively.

Figure 3. Bland-Altman Plot of Cardiac SUV_{peak} for Reader 1



Bland-Altman plots indicated that most of the differences between visits in cardiac SUV_{peak} were relatively close to the mean difference and evenly distributed across 2 SD of the mean.

- The RC estimates for SUV_{max} and SUV_{peak} within readers and between visits were good (**Table 3**)

Table 3. Summary of Between-Visit Repeatability Coefficients for SUV_{peak}

	Reader 1	Reader 2	Reader 3
Mean	6.74	6.75	6.75
wCV, %	13.06	11.57	8.21
95% RC, %	−28.8, 40.5	−26.2, 35.5	−19.6, 24.5

RC is the maximum difference that is likely to occur between repeated measurements.
N=20 subjects/organs with positive amyloid uptake are included in the calculations.
95% RC (%) was calculated on the log-transformed data and exponentiated to determine its limits in percentages.

- Cohen's kappa for cardiac uptake was high at 0.87, 0.87 and 0.79 for Readers 1, 2 and 3, respectively, supporting substantial to almost-perfect intra-rater agreement (**Table 4**)

Table 4. Cohen's Kappa for Intra-Reader Agreement

	Reader	Visit 2		Cohen's kappa (95% CI)
	Reader 1	Negative	Positive	
Visit 1	Negative	4	1	0.87 (0.61-1.00)
	Positive	0	22	
	Reader 2	Negative	Positive	
Visit 1	Negative	4	1	0.87 (0.61-1.00)
	Positive	0	22	
	Reader 3	Negative	Positive	
Visit 1	Negative	5	1	0.79 (0.50-1.00)
	Positive	1	20	

Cohen's kappa values represent the level of agreement between the 2 scans for each radiologist: 0.01-0.20 as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1.0 as almost perfect agreement.[7]

- Fleiss' kappa for inter-rater agreement was 0.92 and 0.83 for cardiac uptake at Visit 1 and Visit 2, respectively, supporting almost perfect inter-rater agreement (**Table 5**)

Table 5. Inter-Rater Agreement for Cardiac Uptake at Visit 1 and Visit 2

Visit	Reader outcomes			Frequency (%)	Fleiss' kappa
	Reader 1	Reader 2	Reader 3		
Visit 1	+	+	+	21 (78)	0.92
	+	+	-	1 (4)	
	+	-	+	0	
	+	-	-	0	
	-	+	+	0	
	-	+	-	0	
	-	-	+	0	
	-	-	-	5 (19)	
Visit 2	+	+	+	21 (78)	0.83
	+	+	-	2 (7)	
	+	-	+	0	
	+	-	-	0	
	-	+	+	0	
	-	+	-	0	
	-	-	+	0	
	-	-	-	4 (15)	

N=27 efficacy-evaluable subjects. Fleiss' kappa values represent the level of agreement among the 3 experts at each visit: 0-0.20 as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1.0 as almost perfect agreement.[7]

Safety Endpoints

- 13 subjects (39.4%) reported a total of 28 TEAEs, which were mild (12/28; 69.2%) or moderate (4/28; 14.3%)
- 1 fatal SAE was reported on Day 28 following the second scan; the SAE, a cerebrovascular accident, was considered not related to ^{124}I-evuzamitide
- There were no TEAEs related to ^{124}I-evuzamitide administration or to KI, and no TEAEs occurred on the day of dosing

Conclusions

- Semiquantitative assessments of ^{124}I-evuzamitide cardiac uptake using SUV_{peak} demonstrated high levels of intra- and inter-rater consistency
- ICC and repeatability coefficients support this conclusion for organ-specific quantitation of radiotracer uptake in the heart following PET/CT imaging of ^{124}I-evuzamitide
- These findings support the potential use of this novel imaging agent to monitor disease progression in patients with cardiac amyloidosis

Abbreviations: **AE**, adverse event; **AL**, amyloid light chain; **ATTR**, amyloid transthyretin; **BMI**, body mass index; **CI**, confidence interval; **CR**, complete response; **CT**, computed tomography; **eGFR**, estimated glomerular filtration rate; **EOS**, end of study; **ICC**, intraclass correlation coefficient; **I**, iodine; **IV**, intravenous; **KI**, potassium iodide; **Max**, maximum; **Min**, minimum; **NT-proBNP**, N-terminal prohormone of brain natriuretic peptide; **PET**, positron emission tomography; **RC**, repeatability coefficient; **SAE**, serious adverse event; **SAF**, safety analysis set; **SD**, standard deviation; **SUV_{mean}**, mean standardized uptake value; **SUV_{max}**, maximum standardized uptake value; **SUV_{peak}**, peak standardized uptake value; **TEAE**, treatment-emergent adverse events; **v**, variant; **VGPR**, very good partial response; **wCV%**, within-subject coefficient of variation; **wt**, wild type.

References

1. Wechalekar AD et al. *Lancet.* 2016;387(10038):2641-2654.
2. Muchtar E et al. *J Intern Med.* 2021;289(3):268-292.
3. Palladini G et al. *Hematology Am Soc Hematol Educ Program.* 2020;2020(1):363-371.
4. Wechalekar AD et al. *Br J Haematol.* 2015;168(2):186-206.
5. Aimo A et al. *Eur J Heart Fail.* 2022;24(12):2342-2351.
6. Paeng JC et al. *Nucl Med Mol Imaging.* 2021;55(2):61-70.
7. Landis JR, Koch GG. *Biometrics.* 1977;33(1):159-174.

Acknowledgments

This study was sponsored by Attralus, Inc. Medical writing support under the guidance of the authors was provided by Karis Moxley, PhD, and Lisa M. Klumpp Callan, PhD, (ApotheCom) and funded by Attralus, Inc.

Disclosures

G. Bell, C. Sherman, A. Yamagami, and I. Hsuie are employees and stockholders of Attralus, Inc. D. Powell, M. Yang, M. Kay, and D. Yoo are consultants of Invicro LLC. D. Behera has served as a paid consultant for Attralus, Inc. M. Covington has served as a paid consultant for Invicro LLC. and as a member of the GE Healthcare Fluoroestradiol Steering Committee and receives royalties from Kindle Direct Publishing. P. H. Kuo is a consultant and/or speaker for Blue Earth Diagnostics, Chimerix, Eli Lilly, Fusion Pharma, General Electric Healthcare, Invicro, Novartis, Radionetics, and Telix Pharmaceuticals. He is a recipient of research grants from Blue Earth Diagnostics and General Electric Healthcare.

Presented at the 28th Annual Scientific Session and Exhibition of the American Society of Nuclear Cardiology (ASNC) 2023; September 29-October 1, 2023; Toronto, Ontario, Canada