(301) COBRA: Assessment of the efficacy of ^{64}Cu-SAR-bisPSMA using histopathology and standard of care imaging as reference standard in patients with biochemical recurrence of prostate cancer following definitive therapy

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Background

- Between 20-40% of patients with prostate cancer (PC) will relapse within 10 years of their primary PC treatment, as identified through rising prostate-specific antigen (PSA) levels.[1] Most relapses will occur within 5 years after definitive therapy.[2] Early diagnosis of biochemical recurrence (BCR) with accurate staging is essential to informing optimal treatment decision-making. Prostate-specific membrane antigen (PSMA) is used as an imaging target in PC. Current PSMA positron emission tomography (PET) agents have high specificity, but low sensitivity.[3-5]
- ^{64}Cu-SAR-bisPSMA may offer several advantages over standard of care (SOC) PSMA PET agents due to the bivalent structure of SAR-**bis**PSMA and longer half-life ($t_{1/2}$) of ^{64}Cu (12.7 h), compared to monovalent PSMA PET agents utilizing ^{18}F and ^{68}Ga ($t_{1/2}$ < 2 h)[3-6] **(Figure 1, Table 1)**.
- Clinical evidence has demonstrated 2-3x higher tumor uptake on same-say imaging and detection of additional PC lesions using ^{64}Cu-SAR-bisPSMA compared to approved PSMA agents.[6,7]
- This led to the development of the COBRA study: a Phase I/II study assessing the safety and efficacy of ^{64}Cu-SAR-bisPSMA in PC patients with BCR and negative or equivocal conventional imaging.

Figure 1. SAR-bisPSMA stylized structure

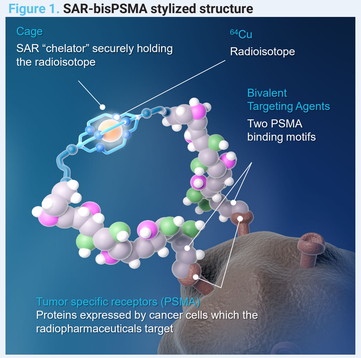


Table 1. Cu-64 characteristics compared to Ga-68 and F-18[3,4]

	Copper-64	Gallium-68	Fluorine-18
Half-life	12.7 h	1.1 h	1.83 h
Typical product shelf-life	Up to 48 h	Up to 4 h	Up to 10 h
Imaging window	1 to 30 h*	50-100 mins	60-90 mins

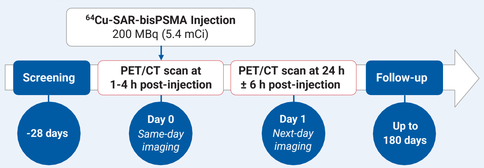
*up to 72 h for dosimetry

Methods

Study Design

Key Eligibility Criteria

- Confirmed adenocarcinoma of prostate with subsequent definitive therapy
- Suspected recurrence of PC based on rising or detectable PSA
- Negative or equivocal findings for PC on conventional imaging per SOC within 60 days prior to Day 0



Primary Objective	Primary Endpoint
To investigate the safety and tolerability of ^{64}Cu-SAR-bisPSMA	Incidence and severity of treatment-emergent Adverse Events and Serious Adverse Events (SAEs) following the administration of ^{64}Cu-SAR-bisPSMA
To investigate the ability of ^{64}Cu-SAR-bisPSMA PET/CT to correctly detect recurrence of PC	Assessed independently for same-day and next-day imaging: • Correct detection rate (CDR): proportion of true positive participants out of all scanned participants who had at least one evaluable reference standard datapoint • Region-level positive predictive value (PPV): proportion of true positive regions out of all positive regions on the ^{64}Cu-SAR-bisPSMA PET/computed tomography (CT) scan with corresponding evaluable reference standard

PET Assessment and Reference Standard:
The ^{64}Cu-SAR-bisPSMA PET/CT scans were interpreted by 3 independent, blinded, central readers. The findings were assessed against a composite Reference Standard (may consist of histopathology, follow-up conventional imaging, and PSA levels) determined by an independent, blinded, central expert panel.
Follow-up SOC PSMA PET scans (interpreted by 2 blinded central readers independent of the ^{64}Cu-SAR-bisPSMA PET readers) were compared.

Hierarchical Reference Standard: The ^{64}Cu-SAR-bisPSMA PET/CT findings will be assessed against a composite reference standard with three levels of evidence:

1. Evaluable histopathology from biopsy or surgery OR in case that histopathology is not available, inconclusive, or negative:
2. Conventional imaging procedures OR if neither histopathology nor conventional imaging are available or informative:
3. Confirmed PSA response following radiation or other salvage focal therapy (no concomitant ADT is given), defined as total PSA decline by ≥ 50% from baseline, confirmed by a second value within 4 weeks, per PCWG3 criteria.

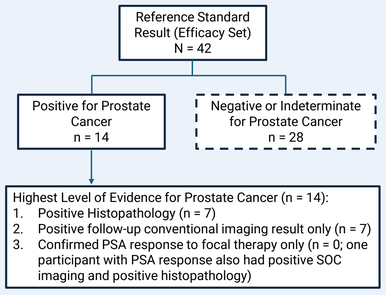
Results

Participant distribution: 52 participants received ^{64}Cu-SAR-bisPSMA (Safety Set) → 50 proceeded to follow-up (Full Analysis Set, FAS) → 8 without reference standard → 42 with reference standard (Efficacy Set)

Table 2. Reference Standard Panel Results (Full Analysis Set)

	Total (N* = 50)
Reference Standard Result, N*	**50**
Positive, n (%)	14 (28)
Negative or Indeterminate, n (%)	28 (56)
Non-evaluable, n (%)	8 (16)
Histopathology Results, n†	**9**
Positive, n (%)	7 (77.8)
Negative, n (%)	2 (22.2)
Follow-Up Conventional Imaging Results, n†	**39**
Positive, n (%)	11 (28.2)
Negative or Equivocal, n (%)	28 (71.8)
PSA Response to Focal Therapy, n†	**8**
Confirmed PSA response, n (%)	1 (12.5)
No Confirmed PSA Response, n (%)	7 (87.5)

*N indicates the total number of participants in the FAS. †n indicates the number of participants with available data for the given parameter



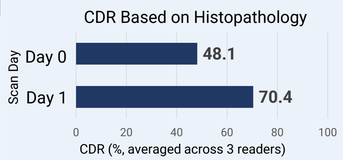
Correct Detection Rate of ^{64}Cu-SAR-bisPSMA was higher on next-day imaging and when using only histopathology as Reference Standard, compared to same-day ^{64}Cu-SAR-bisPSMA and use of conventional follow-up imaging as Reference Standard

- CDR was considerably higher when using the gold standard of histopathology as the reference standard, highlighting the limitations of using less-sensitive methods to verify the ^{64}Cu-SAR-bisPSMA PET findings.
- The CDR results using the composite reference standard (conventional imaging, histopathology, and PSA decline following focal therapy) were substantially impacted by the large number of lesions that were detected, but unable to be biopsied (not clinically appropriate), coupled with the low sensitivity of the conventional imaging scans that were used for the validation of the ^{64}Cu-SAR-bisPSMA scan findings.

Table 3. Participant Level CDR (Reference Standard Comparison)

	^{64}Cu-SAR-bisPSMA Same-day imaging	^{64}Cu-SAR-bisPSMA Next-day imaging
Participant Level CDR using Composite Reference Standard (n = 42)†		
CDR % (95% CI)	19.0-26.2 (8.6-42.0)	26.2-33.3 (13.9-49.5)
Participant Level CDR using Histopathology Only (n = 9)†		
CDR %	44.4-55.6	55.6-77.8
Participant Level CDR using Conventional Imaging Only (n = 39)*†		
CDR %	10.3-20.5	23.1-25.6

*n indicates the number of participants with available data for the given parameter. †Ranges across 3 blinded central readers.
DR, detection rate; CDR, correct detection rate; TP, true positive; N, number of participants



Histopathology confirmed the presence of prostate cancer in lesions identified by ^{64}Cu-SAR-bisPSMA PET in **up to 78%** of cases in which biopsies were obtained

Detection rate on same- and next-day imaging with ^{64}Cu-SAR-bisPSMA was higher than that observed on follow-up conventional imaging by Day 90 and Day 180

Table 4. Detection Rates of Same- and Next-Day ^{64}Cu-SAR-bisPSMA PET and of Follow-Up Conventional Imaging by Day 90 and 180

	^{64}Cu-SAR-bisPSMA Same-day imaging[1] N = 50	^{64}Cu-SAR-bisPSMA Next-day imaging[1] N = 50	Follow-Up Conventional Imaging by Day 90[2] n = 39	Follow-Up Conventional Imaging by Day 180[2] n = 30
Detection Rate, mean	52.7%	70.7%	23%	8.5%
Detection Rate, range	44-58%	58-80%	15-31%	7-10%
95% CI	30-71.8	43.2-90	NA	NA

1. ^{64}Cu-SAR-bisPSMA PET/CT scans interpreted by 3 blinded central readers. Mean and range across the 3 readers. 2. Follow-up conventional imaging scans interpreted by 2 blinded central readers independent of the ^{64}Cu-SAR-bisPSMA central readers. Mean and range across the 2 readers. CI: confidence interval. NA: not applicable.

34%↑ more participants had a positive ^{64}Cu-SAR-bisPSMA scan on next-day (71%) vs. same-day (53%) imaging *(average across 3 readers)*

>80% increase in lesion SUVmax and SUVmean on next-day vs. same-day imaging

>5x higher tumor-to-background ratio on next-day vs. same-day imaging

SUVmean/max and tumor-to-background ratio comparing same-day and next-day imaging. Average increase across 3 readers. The SUVmax, SUVmean and tumor-to-background ratio were assessed in up to 25 lesions per patient on each ^{64}Cu-SAR-bisPSMA scan. Ranges across the readers for same-day and next-day imaging, respectively: SUVmean 6.6-9.9 and 14.7-15.8; SUVmax 13.9-14.0 and 22.2-33.4; tumor-to-background ratio 23.2-25.4 and 118.1-181.7. TBR = SUVmax of the lesions / SUVmean of the gluteus region. SUVmean, mean standardised uptake value; SUVmax, maximum standardised uptake value.

Detection rate of ^{64}Cu-SAR-bisPSMA higher than detection rate of follow-up SOC PSMA PET up to 180 days later in subset of 20 participants

- Follow-up SOC PSMA PET was obtained in 20 participants (13 with ^{68}Ga-PSMA-11 and 7 with ^{18}F-DCFPyL)
- Median time from same-day ^{64}Cu-SAR-bisPSMA imaging to follow-up PSMA PET: 73.5 days (range, 29-180 days)
- More lesions and more participants with a positive scan identified by ^{64}Cu-SAR-bisPSMA vs. SOC PSMA PET, and on next-day vs. same-day imaging
- Results indicate that ^{64}Cu-SAR-bisPSMA is able to identify lesions from 29 days to more than 6 months earlier than SOC PSMA agents

Table 5. Detection Rate and Sum of Lesions Identified in Follow-Up SOC PSMA PET Subset of 20 COBRA participants

	^{64}Cu-SAR-bisPSMA Same-day imaging	^{64}Cu-SAR-bisPSMA Next-day imaging	Follow-Up SOC PSMA PET
Positive scan, n (%)*	14 (70)	18 (90)	12 (60)
Sum of lesions, avg.**	26.3	52.6	20.0

*Number (and percentage) of participants who had a positive scan confirmed by at least 1 reader (3 readers for ^{64}Cu-SAR-bisPSMA, 2 independent readers for follow-up SOC PSMA PET).
**Average of the "sum of lesions" (across readers) in participants with a positive scan for each respective tracer

Pelvic nodal involvement identified by ^{64}Cu-SAR-bisPSMA (negative ^{68}Ga-PSMA-11 PET/CT 175 days later)

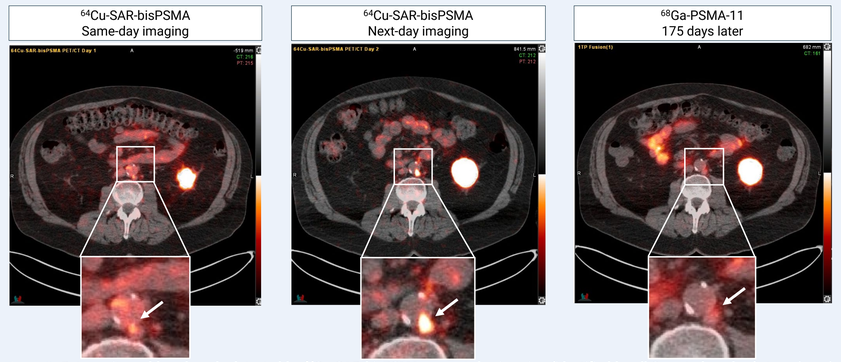


Figure 2. Retroperitoneal lymph node detected by ^{64}Cu-SAR-bisPSMA on next-day imaging (identified by all 3 central readers). Lymph node involvement was not identified on the ^{68}Ga-PSMA-11 scan performed 176 days post-Day 0 (i.e. 175 days post the ^{64}Cu-SAR-bisPSMA PET/CT that detected the LN) according to central read. Histopathology, performed on Day 190, confirmed the presence of prostate cancer in the extra-pelvic lymph node region in this participant. PET/CT fusion. Images below full scans represent inset highlighted on full scans.

Conclusions

The COBRA study showed that ^{64}Cu-SAR-bisPSMA is effective in detecting PC lesions in patients with BCR, with lesions identified in up to 80% of participants with negative or equivocal baseline conventional imaging. More participants with a positive ^{64}Cu-SAR-bisPSMA were identified on next-day imaging vs. same-day imaging. The correct detection rate was considerably higher when using the gold standard of histopathology to verify ^{64}Cu-SAR-bisPSMA PET lesions vs. follow-up conventional imaging, which highlights the limitations of using less-sensitive methods to verify the ^{64}Cu-SAR-bisPSMA PET findings. More lesions were detected using ^{64}Cu-SAR-bisPSMA in a subset of participants who had follow-up SOC PSMA PET up to 180 days later, demonstrating that ^{64}Cu-SAR-bisPSMA may be able to identify lesions earlier than SOC PSMA PET agents. These results have important clinical implications, as the identification of lesions in patients with BCR can inform different treatment pathways. Results from the COBRA trial will be further validated by the upcoming registrational Phase III AMPLIFY trial of ^{64}Cu-SAR-bisPSMA PET in patients with biochemical recurrence of prostate cancer following definitive therapy.

References:
1. Ward JF, Moul JW. *Nat Clin Pract Urol.* 2005; 2(4): 174-82.
2. Pak S et al. *Int J Clin Oncol*. 2019; 24(10): 1238-1246.
3. Locametz. Prescribing Information. Novartis;2023.
4. Pylarify. Prescribing Information. Lantheus; 2023.
5. Posluma. Prescribing Information. Blue Earth Diagnostics; 2023.
6. Lengyelova et al. ASCO, 2023.
7. Nordquist et al. ASCO, 2024.

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