COBRA: Assessment of safety and efficacy of ^{64}Cu-SAR-bisPSMA in patients with biochemical recurrence of prostate cancer following definitive therapy

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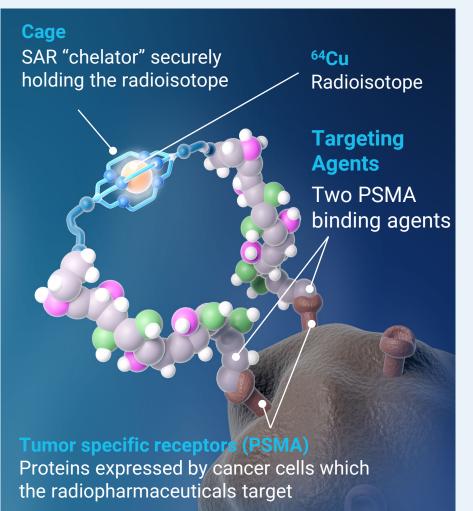
BACKGROUND

- 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 the currently approved PSMA PET agents due to the bivalent structure of SAR-**bis**PSMA and longer half-life ($t_{1/2}$) of ^{64}Cu (12.7h), compared to monovalent PSMA PET agents utilizing ^{18}F and ^{68}Ga ($t_{1/2}$<2h)[3-6] (**Figure 1, Table 1**).

- Clinical evidence has demonstrated 2-3x higher tumor uptake and detection of additional PC lesions using ^{64}Cu-SAR-bisPSMA compared to ^{68}Ga-PSMA-11[6].

- 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 standard of care (SOC) imaging.

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

Figure 1. SAR-bisPSMA stylized structure

Cage
SAR "chelator" securely holding the radioisotope

^{64}Cu
Radioisotope

Targeting Agents
Two PSMA binding agents

Tumor specific receptors (PSMA)
Proteins expressed by cancer cells which the radiopharmaceuticals target

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

^{64}Cu-SAR-bisPSMA Injection
200 MBq (5.4 mCi)

Screening | PET/CT scan at 1-4 h post-injection | PET/CT scan at 24 h ±6 hrs post-injection | Follow-up

-28 days | Day 0 / Same-day imaging | Day 1 / Next-day imaging | Up to 180 days

Primary Objective	Primary Endpoint
To investigate the safety and tolerability of ^{64}Cu-SAR-bisPSMA	Incidence and severity of treatment-emergent Adverse Events (TEAEs) 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 (consisting of histopathology, follow-up SOC imaging and PSA levels) determined by an independent, blinded, central expert panel.

RESULTS

Patient distribution: 52 patients received ^{64}Cu-SAR-bisPSMA (Safety Set) → 2 replacements (protocol deviations) → 50 proceeded to follow-up → 8 without reference standard → 42 with reference standard (Efficacy Set)
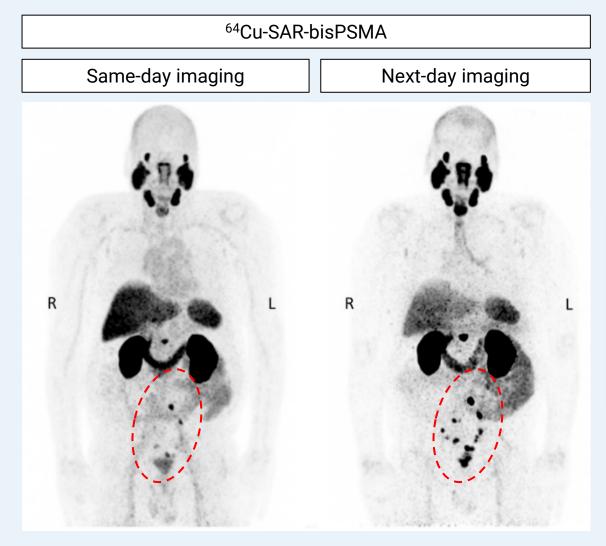
Safety

Table 2. Treatment-Emergent Adverse Events (TEAEs)

Unrelated TEAEs	N (%)
Participants with at least one TEAE	9 (17.3)

Related TEAEs	N (%)
Worsening Type 2 diabetes mellitus	1 (1.9)

- Safety analysis set: all patients who received ^{64}Cu-SAR-bisPSMA, n=52
- Only one related TEAE was reported in one patient (grade 2, worsening of type II diabetes), resolved.

^{64}Cu-SAR-bisPSMA detects more lesions on next-day vs. same-day imaging

^{64}Cu-SAR-bisPSMA — Same-day imaging — Next-day imaging

85% ↑ increase in the total number of lesions, from **70** (same-day) to **129** (next-day imaging) (average across 3 readers)

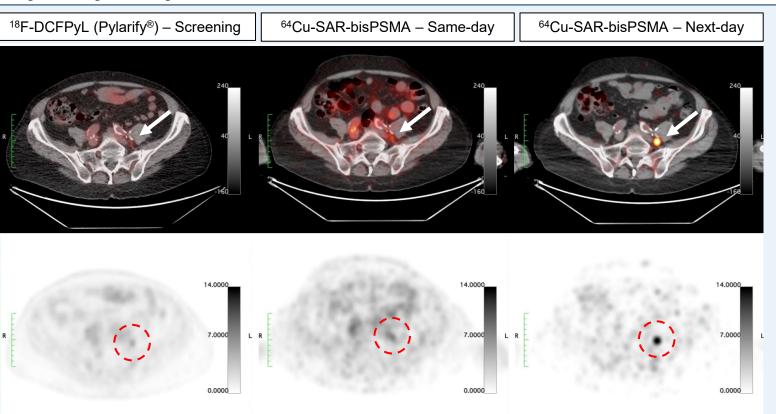**Table 3.** Number of lesions per participant with a positive ^{64}Cu-SAR-bisPSMA scan

Number of lesions per participant	Same-day imaging (n=22-29)	Next-day imaging (n=29-40)
Mean range	2.4-2.8	2.8-4.1
SD range	2.4-3.6	3.1-4.5
Median	1.0	1.0-2.0
Min, Max	1, 15	1, 15
Sum of all lesions	53-80	82-153

The number of lesions per participant data only include patients who had a positive ^{64}Cu-SAR-bisPSMA PET. The table shows the ranges across the 3 readers. The median values across readers was the same on same-day imaging (i.e. 1.0), therefore no ranges are provided.

Figure 2. Next-day imaging identified additional lesions compared to same-day imaging. Same-day ^{64}Cu-SAR-bisPSMA PET showing positive lymph nodes in the pelvic, extra-pelvic (retroperitoneal) and prostatic bed regions, with additional lesions on next-day imaging.

Identification of pelvic lesion by ^{64}Cu-SAR-bisPSMA in a patient with equivocal entry scan using ^{18}F-DCFPyL, Pylarify®

^{18}F-DCFPyL (Pylarify®) – Screening | ^{64}Cu-SAR-bisPSMA – Same-day | ^{64}Cu-SAR-bisPSMA – Next-day

Figure 3. Identification of a lesion in the pelvic region using ^{64}Cu-SAR-bisPSMA on next-day imaging (right), negative on same-day imaging (center) and equivocal on screening ^{18}F-DCFPyL imaging (left). SUVmax of the lesion across scans (arrows in top images and red circles in bottom images) was 2.3, 4.3 and 17.5 (^{18}F-DCFPyL at screening, same-day and next-day imaging with ^{64}Cu-SAR-bisPSMA, respectively). Top images: PET/CT fusion. Bottom images: PET.

^{64}Cu-SAR-bisPSMA imaging led to clinicians changing their intended treatment plan in 48% of the patients

Increase in Detection Rate (DR) and CDR from same-day to next-day imaging

Table 4. Patient level DR, CDR and Region level PPV

^{64}Cu-SAR-bisPSMA PET	Same-day imaging	Next-day imaging
Patient Level DR (N=50)		
Positive patients, n (%)	22-29 (44-58)	29-40 (58-80)
Equivocal patients, n (%)	2-6 (4-12)	0-7 (0-14)
Negative patients, n (%)	15-25 (30-50)	6-21 (12-42)
Patient Level CDR (N=42)		
TP patients, n (%)	9-12 (21.4-28.6)	12-16 (28.6-38.1)
CDR % (95% CI)	21.4-28.6 (10.3-44.6)	28.6-38.1 (15.7-54.4)
Region Level PPV (N=42)		
TP regions, n (%)	9-14 (4.6-7.2)	13-17 (6.7-8.7)
FP regions, n (%)	14-20 (7.2-10.3)	17-35 (8.7-18.0)
PPV (95% CI)	39.1-44.8 (19.7-64.3)	32.7-43.3 (20.3-62.6)

The table shows the ranges across the 3 reader (including values within brackets). DR: detection rate; CDR: correct detection rate; PPV: predictive positive value; TP: true positive; FP: false positive. N: number of participants.

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

- Specificity of PC detection in the pelvic lymph nodes remained high at 95% and 85% (same-day vs. next-day imaging, average across readers).

- The CDR and PPV results 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 SOC scans that were used for co-localization.

^{64}Cu-SAR-bisPSMA demonstrated higher uptake and contrast in lesions on next-day vs. same-day imaging and detected lesions in the 2-millimeter range

SUVmean and SUVmax in lesions detected by ^{64}Cu-SAR-bisPSMA — ■ Day 0 ■ Day 1

TBR of lesions detected by ^{64}Cu-SAR-bisPSMA — ■ Day 0 ■ Day 1

^{64}Cu-SAR-bisPSMA PET — Same-day imaging | Next-day imaging

>80% ↑ increase in **mean SUVmean and SUVmax** (same-day vs. next-day imaging)

>5x ↑ increase in **mean TBR** (same-day vs. next-day imaging)

Figure 5. Pelvic lymph nodes showing uptake of ^{64}Cu-SAR-bisPSMA on next-day imaging (arrows, B). Blue arrow: lesion size 3.8 mm x 4.4 mm, SUVmean 20.6, SUVmax 22.1 and TBR 130.1. Green arrow: lesion size also 3.8 mm x 4.4 mm, SUVmean 11.9, SUVmax 12.8 and TBR 75.3. Red arrow: lesion size >5 mm.
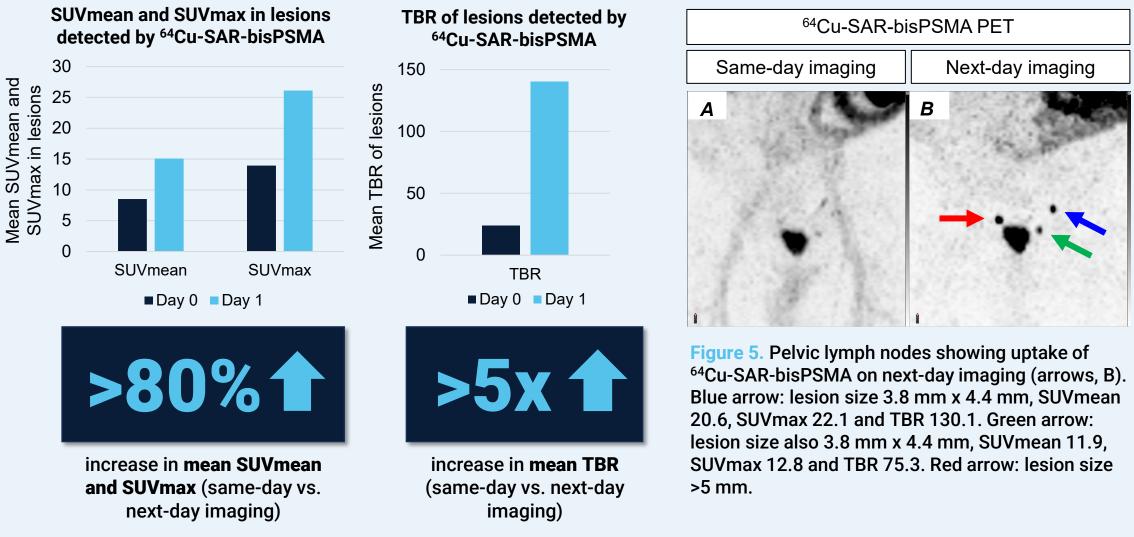
Figure 4. SUVmean/max and TBR comparing same-day (Day 0) and next-day (Day 1) imaging. Average increase across 3 readers. SUVmean: mean standardised uptake value. SUVmax: maximum standardised uptake value. TBR: tumour-to-background ratio. The SUVmax, SUVmean and TBR were assessed on each ^{64}Cu-SAR-bisPSMA 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; TBR 23.2-25.4 and 118.1-181.7. TBR = SUVmax of the lesions / SUVmean of the gluteus region.

Conclusions

- COBRA showed for the first time that ^{64}Cu-SAR-bisPSMA is safe and effective in detecting PC lesions in patients with BCR.
- Only one TEAE was related to ^{64}Cu-SAR-bisPSMA (resolved).
- Next-day ^{64}Cu-SAR-bisPSMA PET localised disease in up to 80% of patients with negative or equivocal SOC imaging at study entry, detecting lesions as small as 2 mm.
- More lesions and more patients with a positive scan were identified on ^{64}Cu-SAR-bisPSMA PET compared to SOC scans, and on next-day vs. same-day imaging.
- Higher uptake and contrast was observed in lesions on the next-day vs. same-day imaging. These findings have important clinical implications as the identification of additional and small lesions can inform different treatment pathways for patients with BCR of PC.

ClinicalTrials.gov Identifier: NCT05249127. This study is sponsored by Clarity Pharmaceuticals Ltd.
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