ONE-YEAR CHRONIC KIDNEY DISEASE OUTCOMES IN PATIENTS WITH HEAD AND NECK CANCER TREATED WITH AVASOPASEM MANGANESE: A PRESPECIFIED ANALYSIS FROM ROMAN

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Background

- Cisplatin-induced AKI, AKD, and CKD are caused by increased production of reactive oxygen species, notably superoxide, in conjunction with alterations in mitochondrial electron transport chain complex activities in renal tubules[1,2]
- These pathologies can be alleviated by increasing superoxide dismutase activity, which decreases superoxide[1]
- The investigational new drug avasopasem manganese (known as avasopasem), a selective dismutase mimetic, ameliorates cisplatin-induced kidney injury in murine models[2]
- Preclinical results demonstrate avasopasem does not interfere with cisplatin anticancer activity[3]
- Retrospective analysis of 1-year kidney function in a limited subset of patients treated in a randomized, placebo-controlled phase 2b trial of avasopasem to reduce SOM from CRT suggested avasopasem may preserve kidney function compared to placebo[4]

GTI-4419-301: The ROMAN Trial (NCT03689712)

- ROMAN is a phase 3 randomized, placebo-controlled double-blind study of avasopasem for the reduction of SOM in patients with locally advanced, nonmetastatic HNC undergoing SOC CRT (**Figure 1**)
- Avasopasem in combination with CRT demonstrated meaningful reduction in SOM across multiple endpoints vs placebo (**Figure 2**), with adverse events comparable between treatment groups (**Figure 3**)[5]

Figure 1. ROMAN Study Design and Eligibility Criteria

Population	• Oral cavity/oropharynx tumor • Locally advanced, squamous cell • Eligible for SoC: 7 weeks IMRT + cisplatin
Treatment	• Avasopasem 90 mg or placebo • 60-minute IV infusion, Mon–Fri • Ending ≤60 min pre-RT
Stratification factors	• Surgery status: post-op or definitive • Cisplatin schedule: q3wks or weekly

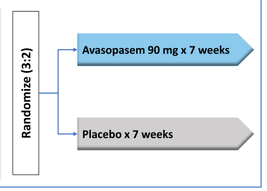
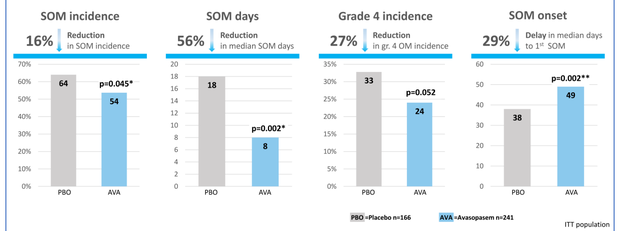
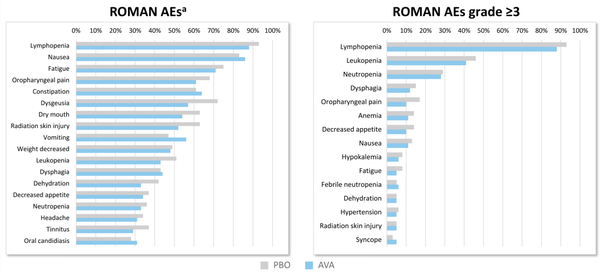


Figure 2. ROMAN Results Across Key SOM Endpoints



* Statistical significance per statistical analysis plan for this phase 3 trial.
** Time to onset was an exploratory endpoint.

Figure 3. ROMAN Most Frequent Adverse Events



[a] ITT population: 166 patients on placebo, 241 on 90 mg avasopasem.

Methods

- Prospectively defined exploratory analysis of ROMAN:
  - Effects of avasopasem on kidney function throughout the first year post-CRT
    - eGFR assessed every 3 months for 1 year following 7 weeks of CRT
  - Incidence of grade 3+ CKD as determined by the proportion of patients with an estimated eGFR <60 mL/min/1.73m^2 at the 1-year visit
    - Analyzed by the Cochran-Mantel-Haenszel test

REFERENCES
1. Mapuskar KA et al. Mitochondrial superoxide dismutase in cisplatin-induced kidney injury. *Antioxidants (Basel)* 2021;10:1329; **2.** Mapuskar KA et al. Persistent increase in mitochondrial superoxide mediates cisplatin-induced chronic kidney disease. *Redox Biol* 2019;20:98–106; **3.** Mohanty AJ et al. Abstract 2929: GC4419 enhances the response of non-small cell lung carcinoma cell lines to cisplatin and cisplatin plus radiation through a ROS-mediated pathway. *Cancer Res* 2018;78:2929; **4.** Mapuskar KA et al. Avasopasem manganese (GC4419) protects against cisplatin-induced chronic kidney disease: An exploratory analysis of renal metrics from a randomized phase 2b clinical trial in head and neck cancer patients. *Redox Biol* 2023;60:102599; **5.** Anderson CM et al. ROMAN: Phase 3 trial of avasopasem manganese (GC4419) for severe oral mucositis (SOM) in patients receiving chemoradiotherapy (CRT) for locally advanced, nonmetastatic head and neck cancer (LAHNC). Presented at ASCO; June 3–7, 2022.

DISCLOSURES
BGA reports grant/research support from Galera Therapeutics, Inc (Galera); **DRS** reports he or his institution received grant/research support from Galera and patents/royalties/other intellectual property from Galera; **KAM** reports grant/research support and patents/royalties/other intellectual property from Galera; **DZ-O** reports patents/royalties/other intellectual property from IP; **RAB** is an employee of and holds stock/other ownership interests with Galera; **EK** is an employee of and holds stock/other ownership interests with Galera; **CMA** reports institutional research funding from and uncompensated relationships with Galera.

ABBREVIATIONS
AE, adverse event; AKD, acute kidney disease; AKI, acute kidney injury; AVA, avasopasem manganese; BUN, blood urea nitrogen; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; CRT, chemoradiation therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; eGFR, estimated glomerular filtration rate; HNC, head and neck cancer; HPV, human papillomavirus; IMRT, intensity-modulated radiation therapy; ITT, intent to treat; IV, intravenous; MMRM, mixed-effects model repeated measures; OM, oral mucositis; PBO, placebo; Q3W, once every 3 weeks; QW, once every week; RT, radiation therapy; SAE, serious AE; sCr, serum creatinine; SD, standard deviation; SOC, standard of care; SOM, severe OM; Tx, treatment.

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Results

Patient Population

- ROMAN phase 3 trial ITT population: 407 patients
  - Avasopasem (N=241) vs placebo (N=166)
- Baseline patient characteristics were balanced between treatment groups (**Table 1**)

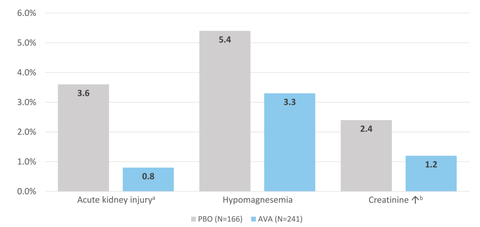
Table 1. Patient Characteristics

Characteristic	AVA 90 mg (n=241)	PBO (n=166)	All patients (N=407)
Sex, n (%)			
Male	202 (84)	149 (90)	351 (86)
Female	39 (16)	17 (10)	56 (14)
Age, years			
Mean (SD)	60.4 (9.37)	61.2 (8.64)	60.8 (9.08)
Median (range)	61 (32–81)	61 (34–84)	61 (32–84)
ECOG PS, n (%)			
0	186 (77)	115 (69)	301 (74)
1	54 (22)	50 (30)	104 (26)
2	1 (<1)	1 (1)	2 (<1)
Tumor site, n (%)			
Oropharyngeal	194 (80)	141 (85)	335 (82)
Oral cavity	38 (16)	21 (13)	59 (14)
Unknown	9 (4)	4 (2)	13 (3)
Treatment type, n (%)			
Definitive	195 (81)	134 (81)	329 (81)
Postoperative	46 (19)	32 (19)	78 (19)
Cisplatin schedule, n (%)			
Every 3 weeks	102 (42)	74 (45)	176 (43)
Weekly	139 (58)	92 (55)	231 (57)

Renal Outcomes From ROMAN

- Reduced incidence of cisplatin-related renal adverse events during treatment with avasopasem (**Figure 4**)

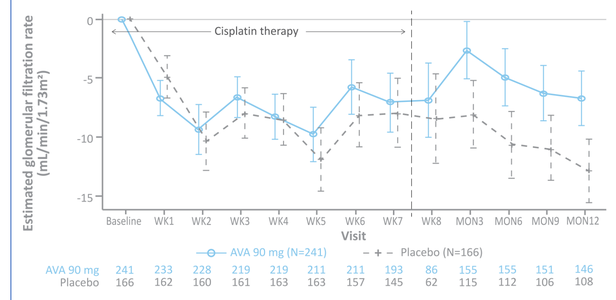
Figure 4. Cisplatin Renal Grade 3+ AEs



[a] Grade 3+ AKI is defined as hospitalization required.
[b] Grade 3+ elevated creatinine is >3x baseline or >3-6 ULN.

- Lesser mean reduction from baseline in eGRF with avasopasem (**Figure 5**)
- Significant improvements in preservation of eGFR (p=0.0008) with avasopasem compared to placebo

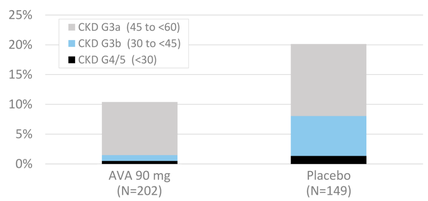
Figure 5. Mean Change in eGFR From Baseline by Visit



Least squares mean change from baseline were generated using an MMRM analysis with the parameters treatment, visit, and treatment-by-visit interaction as factors and baseline value as covariate. Error bars represent standard errors.
eGFR was calculated using the CKD-EPI equation.

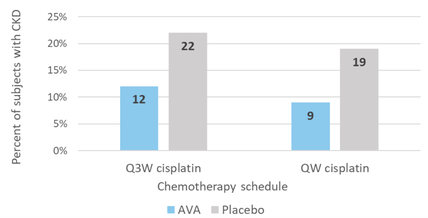
- Significant reduction in incidence of grade 3+ CKD according to KDIGO criteria (eGFR <60 mL/min/1.73m^2) at 1-year follow-up with avasopasem compared to placebo (relative risk 0.55, p=0.0043, **Figure 6**)

Figure 6. Grade 3+ CKD According to KDIGO Criteria at 1 Year



- Reduced incidence of grade 3+ CKD with avasopasem among patients receiving Q3W therapy and for patients receiving QW therapy (**Figure 7**)

Figure 7. Grade 3+ CKD at 1 Year by Chemotherapy Schedule



Conclusions

- Avasopasem appears to reduce cisplatin-related kidney damage in the study population during treatment and through 1-year follow-up
- Study results carry significance beyond CRT for HNC and may potentially impact platinum-containing regimens in other cancers; further research is required

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