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*Results from EVITA, a phase 2 randomized, placebo-controlled trial*

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ORIGINAL ARTICLE

# Oral vitamin C supplementation in patients with clonal cytopenia of undetermined significance or lower-risk myeloid malignancies: Results from EVITA, a phase 2 randomized, placebo-controlled trial

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## Abstract

**Background:** Vitamin C (VitC) is a cofactor for TET enzymes involved in DNA demethylation and epigenetic regulation. Mutations in *TET2* are common drivers of leukemia. Preclinical studies suggest that VitC may delay leukemia progression. This study aimed to evaluate the biological activity, safety, and clinical impact of oral VitC in patients with clonal cytopenia of undetermined significance (CCUS) or lower risk myeloid malignancies.

The second, third, and fourth authors contributed equally to this article.

The last two authors contributed equally to this article.

This trial was registered at ClinicalTrials.gov (NCT03682029).

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**Methods:** EVITA (Epigenetics, Vitamin C, and Abnormal Hematopoiesis) was a double-blind, randomized, placebo-controlled, phase 2 trial conducted in Denmark and the United States. Adults with CCUS or lower risk myeloid malignancies not receiving anticancer therapy were randomly assigned (1:1) to receive oral VitC (1000 mg/day) or placebo for 12 months, followed by long-term follow-up. The primary end point was the median clonal growth rate from baseline to end of treatment. EVITA was registered at ClinicalTrials.gov (NCT03682029), and is now completed.

**Results:** Between November 1, 2017, and September 28, 2022, 109 patients were enrolled (VitC, $n = 55$; placebo, $n = 54$). Although the primary end point, median clonal growth rate, did not differ between groups (−0.016; 95% CI, −0.096 to 0.064; $p = .70$), secondary outcomes included differences in inflammatory cytokine trajectories and fewer serious adverse events in the VitC group versus placebo (18 of 55 [33%] vs. 30 of 53 [57%]). In exploratory analyses, overall survival was significantly longer with VitC (hazard ratio, 0.35; 95% CI, 0.17 to 0.71; $p = .0025$).

**Conclusions:** These findings suggest oral VitC as a safe, biologically active intervention in patients with early-stage myeloid malignancies and precursor conditions. A phase 3 trial is warranted.

**KEYWORDS**
clonal cytopenia, interception, myeloid malignancies, precursor conditions, randomized controlled trial

## INTRODUCTION

Myelodysplastic syndromes (MDS) are myeloid malignancies originating in hematopoietic stem cells (HSCs), and are characterized by failure of the bone marrow to sustain normal hematopoiesis. An acquired mutation in HSCs giving rise to clonal hematopoiesis typically initiates disease. Epigenetic regulator genes are among the most commonly mutated (e.g., *TET2*, *ASXL1*, and *DNMT3A*),[1] and acquired epigenetic changes are a hallmark of MDS.[2, 3] MDS tend to worsen over time, with a risk of progression to acute myeloid leukemia (AML). The only curative therapy for MDS is allogeneic hematopoietic stem cell transplantation, for which older patients with comorbidities are not eligible.

In recent years, clonal cytopenia of undetermined significance (CCUS) was identified as a precursor condition for myeloid malignancies. CCUS is diagnosed when myeloid malignancy–related somatic mutations are detected in patients referred with persistent unexplained cytopenia and diagnostic morphological findings are absent.[4] Patients with CCUS are typically managed with a watch-and-wait strategy under clinical follow-up, as no interception strategy is currently available.

The potential of vitamin C (ascorbate) for cancer treatment has been debated for half a century; results have been ambiguous, in part attributable to methodological discrepancies between studies, weaknesses in study designs, and testing in diverse advanced cancers.[5] Renewed interest in vitamin C as a potential cancer therapeutic emerged after its role in epigenetic regulation and cellular differentiation was proposed more than a decade ago.[6] Subsequent studies identified vitamin C as a cofactor for iron-dependent dioxygenases that catalyze the demethylation of repressive histone marks[7] and promote the oxidation of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC) via TET enzymes[8]—an initiating step in active DNA demethylation.

Early advocacy for high-dose vitamin C intravenously (iv) followed by oral administration to patients with advanced cancers[9, 10] lacked supporting evidence, given that randomized trials showed no efficacy of oral vitamin C in patients with advanced malignancies.[11, 12] However, physiological levels of vitamin C in vitro blocked oncogenic transformation of immortalized mouse embryo cells by aromatic hydrocarbons when administered before transformation, which suggested that early exposure is critical.[13] This is supported by a study showing that vitamin C–depleted mice exhibited accelerated leukemogenesis on transplantation with leukemic cells whereas oral supplementation delayed progression, particularly when initiated before rather than after transplantation.[14] Notably, vitamin C deficiency is common among patients with hematological malignancies.[15, 16] Thus, a role of vitamin C is implied not only in epigenetic regulation but also in the evolution and interception of early-stage myeloid malignancies.

Here, we report the results of a phase 2 randomized placebo-controlled trial (RCT) conducted in Denmark and the United States

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to evaluate the biological activity, safety, and clinical outcomes of oral vitamin C (1000 mg/day for 12 months) in 109 adult patients with CCUS or lower risk myeloid malignancies.

## MATERIALS AND METHODS

### Study design

EVITA (Epigenetics, Vitamin C, and Abnormal Hematopoiesis) is an investigator-initiated, international, multicenter, parallel-group, double-blind, phase 2 RCT that enrolled patients from four sites in Denmark ($n = 3$; enrollment years 2017–2022) and the United States ($n = 1$; 2019–2022).

The study compared oral vitamin C supplementation, 1000 mg/day for 12 months, versus placebo in 109 patients with CCUS or lower risk myeloid malignancies. Any prior vitamin C supplementation was discontinued on inclusion and not permitted during the treatment phase. Otherwise, patients were advised to maintain their regular diet.

All patients were followed for disease progression and overall survival from the end of treatment until death, withdrawal of consent, loss to follow-up, or end of study (last patient's last visit). During this observation phase, no postprotocol therapy was administered, and there were no restrictions on vitamin C supplementation or other treatments. Supporting Information S1: Figure S1 provides an overview of the study course.

The initial 2:1 allocation was adjusted after enrollment of the first quarter of patients to achieve an overall 1:1 allocation in the full cohort (see Supporting Information S1: Table S1 for major protocol amendments and rationale).

The study was approved by the Danish Research Ethics Committee (H-16022249/H-22030393) and the Institutional Review Board, University of Southern California Norris Comprehensive Cancer Center (HS-19-00084), and all patients provided written informed consent. The EVITA trial is registered at ClinicalTrials.gov (NCT03682029; https://clinicaltrials.gov/study/NCT03682029).

### Population

Inclusion criteria were age ≥ 18 years; either CCUS (criteria are listed in Supporting Information S1: Table S2), MDS of low or very low risk by the Revised International Prognostic Scoring System (score ≤ 3),[17] or myelodysplastic/myeloproliferative neoplasms (MDS/MPN), including chronic myelomonocytic leukemia (CMML) 0 or 1, according to the 2016 World Health Organization (WHO) classification[18]; a somatic mutation in hematopoietic cells with a variant allele frequency (VAF) of ≥5% in genes recurrently mutated in myeloid malignancies (Supporting Information S1: Table S3); and bone marrow blasts of <5% (or <10% in CMML).

Exclusion criteria were pregnancy; allergic hypersensitivity to vitamin C; urinary tract stones within the preceding year; unwillingness to discontinue all additional vitamin C supplementation, including multivitamins, during study treatment; therapeutic radiation or other anticancer treatment, including investigational agents, within the preceding 6 months; or inability to comply with study requirements.

Eligible participants included both newly and previously diagnosed patients. Use of erythropoiesis-stimulating agents and granulocyte colony-stimulating factor (G-CSF) was permitted.

We conducted a broad screening that also included individuals referred to the participating hematology departments for evaluation of unexplained cytopenia and suspected MDS. Participant recruitment details are provided in Supporting Information S1 (p 6).

### Randomization and masking

Randomization was performed centrally via a block scheme, with permuted variable block sizes stratified by hospital region. The identity of the treatments was concealed with study preparations identical in packaging, labeling, schedule of administration, appearance, odor, and taste. Allocation data were concealed from participants, health care providers, outcome assessors, and data analysts until study completion and final data analysis to maintain blinding. See also Supporting Information S1 (p 6).

### Procedures

Patients received oral vitamin C (ascorbic acid) 1000 mg once daily (two 500-mg capsules) or a matching placebo for up to 12 months or until study treatment was discontinued for any reason, followed by long-term follow-up. Oral vitamin C is classified as a nutritional supplement, not a drug, by both the Danish Medicines Agency and the US Food and Drug Administration.

Study visits and biobank sampling were conducted every 3 months at five time points from baseline (pretreatment) to the end of treatment at 12 months.

Peripheral blood tests and biobanking were conducted at all five study visits. Bone marrow investigation, including morphology and G-banding karyotyping, was performed pretreatment (within 4 months before randomization) and at 12 months. Bone marrow aspirates were collected for biobanking alongside bone marrow investigations and additionally at 3 months. Detailed procedures are in Supporting Information S1 (p 7).

### Outcomes

The primary end point was the median (i.e., the 0.5 quantile) clonal growth rate, which was based on the median per-patient growth rate across all mutations, assessed from baseline to end of treatment (12 months, or 3 months in the case of early discontinuation). Clonal growth rate for each unique variant was calculated as ln(VAF at end of treatment/VAF at baseline) per year. Paired baseline and end-of-

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treatment DNA samples for next-generation sequencing (NGS) were preferentially obtained from bone marrow $CD34^+$ hematopoietic stem and progenitor cells (HSPCs).

Secondary end points included plasma vitamin C concentration, cytokine and chemokine levels, global 5-mC, global 5-hmC/5-mC ratio, disease progression, hematological improvement and hematological progression (defined in Supporting Information S1, pp 9–10), and safety.

Endpoint definitions and time points are detailed in Supporting Information S1 (pp 8–10).

Overall survival was analyzed post hoc as an exploratory end point; it was planned before the end of the study but not included in the protocol.

Exploratory subgroup analyses were limited to three factors, selected on the basis of biological and clinical relevance: *TET2* or *IDH1/2* mutation status (mutant vs. wild type, given that mutations in any of these genes impair TET-mediated hydroxymethylation); baseline diagnosis (CCUS vs. MDS vs. MDS/MPN); and baseline plasma vitamin C concentration (≥median vs. <median).

Additional preplanned translational analyses, including CpG site–specific DNA methylation analysis, were performed and will be reported separately.

## Laboratory analyses

Laboratory analyses as well as diagnostic workup and biobanking procedures are described in depth in Supporting Information S1 (pp 10–16).

## Mutation analysis

Somatic variants were identified via targeted NGS of 151 genes recurrently mutated in clonal hematopoiesis, MDS, and AML, as specified by the International Working Group for Prognosis in MDS (Supporting Information S1: Table S4). DNA samples were sequenced at a median coverage of ~1600×, and processed via a validated in-house analysis pipeline. Analyses were restricted to pathogenic variants in 38 genes by applying predefined gene-specific filtering. Common single-nucleotide polymorphisms (>1% minor allele frequency) and variants with an allele frequency of <2% were excluded. Full mutation analysis methods and variant inclusion criteria are detailed in Supporting Information S1 (p 10, Supporting Information S2, and Supporting Information S3) and Supporting Information S1: Table S4.

## Vitamin C measurement

Within 10 min of sample collection, plasma was acidified by mixing with an equal volume of 10% meta-phosphoric acid solution and then centrifuged, and the supernatant was stored immediately at −80°C/−112°F. Total plasma vitamin C (ascorbate plus dehydroascorbic acid) was quantified in peripheral blood and bone marrow samples by high-performance liquid chromatography, modified for diode array detection. Study participants were instructed to abstain from vitamin C–containing foods, beverages, and study medication from midnight before sampling. See also Supporting Information S1 (p 14).

## Cytokine and chemokine profiling

Peripheral blood plasma was frozen and stored at −80°C/−112°F within 10 min of blood collection. Nineteen plasma cytokines and chemokines involved in inflammation, chemotaxis, and immune regulation were measured in duplicate via multiplex electrochemiluminescence assays (Meso Scale Discovery). Details are provided in Supporting Information S1 (p 14).

## Global DNA methylation and hydroxymethylation analysis

Global 5-mC and 5-hmC levels were quantified in genomic DNA from $CD34^+$ HSPCs via liquid chromatography–mass spectrometry. Analyte concentrations were normalized to total deoxyguanosine, and 5-hmC levels were also normalized to 5-mC. Full methodological details are in Supporting Information S1 (pp 14–16).

## Safety

Safety was assessed by the incidence of adverse events (AEs) and serious adverse events (SAEs) during treatment, classified via Medical Dictionary for Regulatory Activities, version 27.0[19] and graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[20] Safety assessment is detailed in Supporting Information S1 (p 17).

Laboratory data were centrally generated; all outcomes were centrally assessed, except for safety events, which were reported locally.

## Statistical analysis

A formal sample size calculation was not performed, given that no prior data were available to estimate the primary end point effect size. At the time of study design, clonal growth dynamics in CCUS—first described in 2015—had not been characterized. EVITA was designed as an exploratory phase 2 RCT to evaluate the biological activity, safety, and selected clinical outcomes of oral vitamin C across key subgroups, with a pragmatic target of at least 50 participants per treatment group.

The primary end point was analyzed in all patients with a follow-up sample and at least one detectable somatic mutation at baseline

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or end of treatment. Secondary end points included measures of biological and epigenetic activity, analyzed on the basis of sample availability, and clinical outcomes, assessed in the intention-to-treat (ITT) population, which comprised all randomized patients by assigned treatment group. Safety analyses included all patients who received at least one dose of study medication. Overall survival was analyzed as an exploratory, post hoc end point in the ITT population. The number of patients included in each analysis is specified in the Results section and Figure 1.

Median clonal growth rates (the primary end point) were compared via quantile regression (R package quantreg, version 6.1),[21] with 95% confidence intervals (CIs) estimated via the emmeans package.[22]

To control for multiple testing, false discovery rate (FDR) correction was applied for the cytokine analysis and separately for subgroup analyses within each end point when $p$ values were reported. Where FDR correction was not applicable, $p$ values are omitted to avoid overinterpretation.

Statistical analyses were performed with R, version 4.4.2 (https://cran.r-project.org/), and are described in depth in Supporting Information S1 (pp 17–18).

## RESULTS

### Patients

Screening and enrollment began on November 1, 2017, and were completed on September 28, 2022. The end of the study, defined as the last patient's last visit on September 27, 2023, was the clinical data cutoff. A Consolidated Standards of Reporting Trials flow diagram is shown in Figure 1. The high screening-to-enrollment ratio largely reflects the broad screening procedure. We enrolled 109 patients at Copenhagen University Hospital–Rigshospitalet ($n = 81$), Copenhagen University Hospital–Herlev ($n = 15$), and Aalborg University Hospital ($n = 5$) in Denmark, and the University of Southern California Norris Comprehensive Cancer Center ($n = 8$) in the United States. A total of 54 patients were randomly assigned to receive placebo, and 55 patients were assigned to receive oral vitamin C.

In the placebo group, 12 of 54 patients (22%) discontinued study treatment for any reason before the protocol-defined end of treatment at 12 months, compared to nine of 55 patients (16%) in the vitamin C group (Figure 1). The most common reason for discontinuation across the overall cohort was progression to higher-risk myeloid malignancies, which necessitated anticancer therapy and withdrawal of study treatment. Discontinuation as a result of AEs was infrequent, with it occurring in one patient (2%) in the placebo group and three patients (5%) in the vitamin C group.

Key baseline characteristics of all randomized participants, tabulated by treatment group, are summarized in Table 1. The placebo group had a slightly higher median age, more male patients, more patients with multilineage cytopenia, and lower blood counts, whereas the vitamin C group had a higher mutational burden and poorer disease prognostic scores (as assessed by the International Prognostic Scoring System–Molecular [1] and the CMML-specific Prognostic Scoring System–Molecular [23]).

### Biological and epigenetic outcomes

At baseline, 57% (62 of 109) of participants had blood plasma vitamin C concentrations in the deficient or inadequate ranges[24] (Table 1; Figure 2A). Of those with adequate levels[24] at baseline, half (25 of 47; 53%) were taking supplements before inclusion. Oral vitamin C rapidly corrected deficiency by increasing median plasma levels from 45.85 μmol/L (interquartile range [IQR], 29.80–69.12 μmol/L) at baseline to 81.90 μmol/L (IQR, 67.08–99.57 μmol/L) at 12 months ($p < .0001$; Figure 2B,C) (i.e., plasma saturation). In contrast, the placebo group showed no significant change (43.75 μmol/L [IQR, 22.20–60.39 μmol/L] at baseline vs. 48.73 μmol/L [IQR, 20.56–58.21 μmol/L] at 12 months; $p = .88$). Notably, plasma vitamin C dynamics indicated that participants in both treatment groups generally adhered to the protocol (Figure 2C), consistent with high patient-reported compliance (Supporting Information S1: Table S5). Spearman correlation analyses showed strong concordance between plasma vitamin C concentrations in peripheral blood and bone marrow across all time points (baseline, 3 months, and 12 months; all $p < .0001$; Spearman $\rho \geq 0.79$; Supporting Information S1: Figure S2). Correlation analyses of baseline vitamin C concentration with dietary intake, supplementation, smoking, and body mass index are in Supporting Information S1 (p 21).

Results for the primary end point are shown in Figure 3. The median clonal growth rate was 0.046 (95% CI, −0.011 to 0.10) per year in the placebo group and 0.030 (95% CI, −0.027 to 0.087) in the vitamin C group, with a between-group difference of −0.016 (95% CI, −0.096 to 0.064; $p = .70$), which indicated no difference between treatment groups. These rates correspond to median proportional increases in VAF of 4.6% (95% CI, −1.05% to 10.24%) per year in the placebo group and 3.03% (95% CI, −2.65% to 8.70%) in the vitamin C group. Plots comparing median clonal growth rates for the five most frequently mutated genes in the cohort (*TET2*, *SRSF2*, *DNMT3A*, *SF3B1*, and *ZRSR2*) are presented in Supporting Information S1: Figure S3 (all FDR-corrected $p > .99$), with exploratory subgroup analyses of the primary end point across clinical and biological strata shown in Supporting Information S1: Figure S4. The baseline somatic mutational landscape of the study cohort is depicted in the oncoplot shown in Supporting Information S1: Figure S5. A complete list of curated somatic variants is provided in Supporting Information S4 .

To evaluate whether vitamin C may modulate inflammation, we assessed changes in 19 cytokines and chemokines in blood plasma. Six analytes showed significantly different changes from baseline to end of treatment between treatment groups, after correction for multiple testing (Figure 4). IL-6, IL-10, CXCL10, macrophage colony-stimulating factor (M-CSF), and G-CSF increased more in the placebo group than in the vitamin C group, whereas RANTES/CCL5 increased more in the vitamin C group. Supporting Information S1: Figure S6

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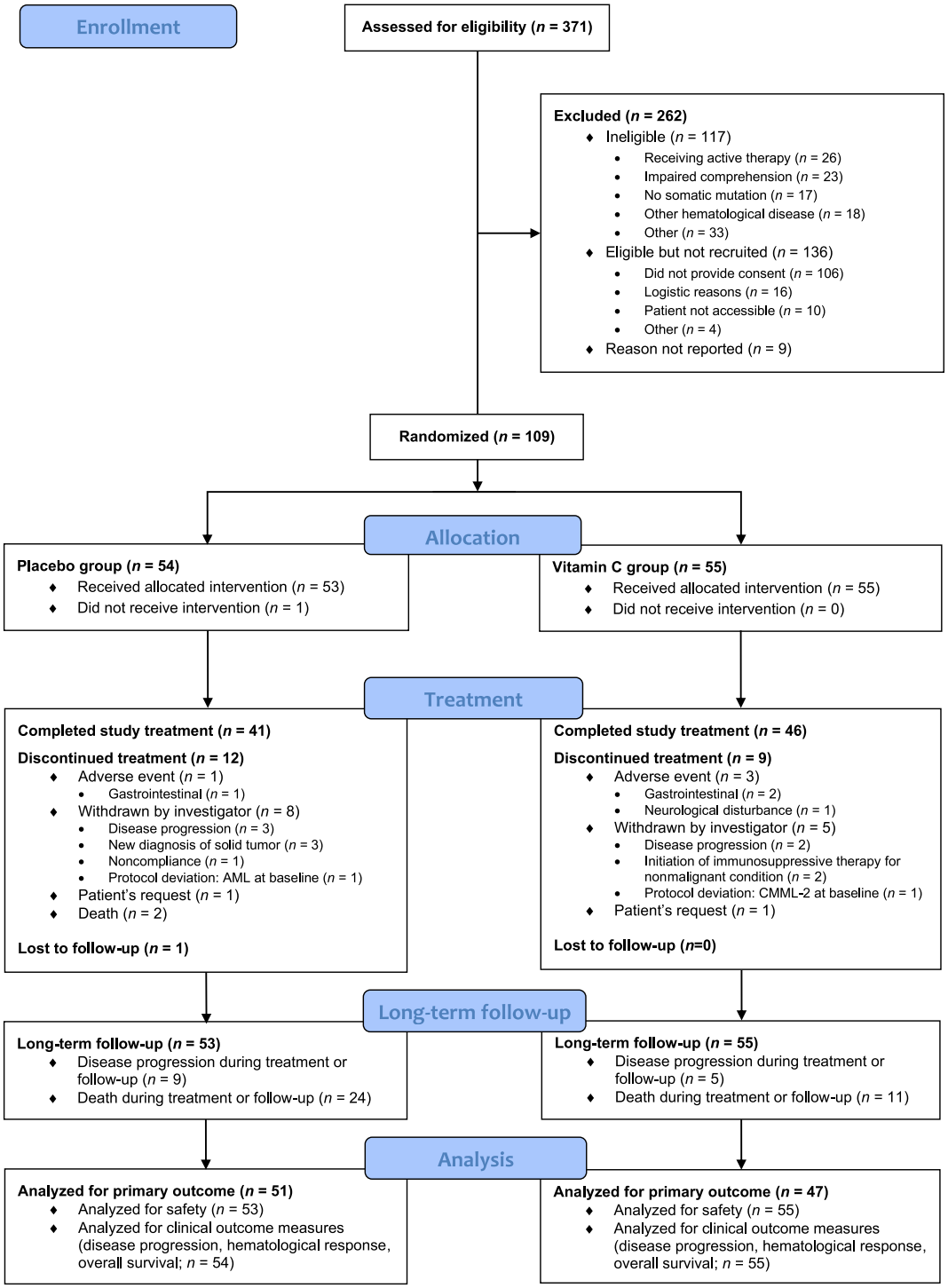


**FIGURE 1** EVITA trial profile. Screening, randomization, treatment, long-term follow-up, and analysis in the EVITA study. Unexpectedly, three participants in each group were later found not to meet diagnostic eligibility criteria on the basis of baseline bone marrow assessments or panel-based next-generation sequencing conducted as part of the study evaluations. In the placebo group, one had isolated monocytosis associated with a germline *NF1* mutation, one had MDS-EB-1, and one had AML. In the vitamin C group, one participant had idiopathic cytopenia of undetermined significance, one had CMML-2, and one had MDS-EB-1. The participants with AML and CMML-2 discontinued study treatment within 2 months to begin anticancer therapy, whereas the others completed the study treatment course. Two additional eligibility-based protocol deviations were identified retrospectively: one patient in each group had no detectable somatic mutations by panel-based sequencing but still met the 2016 World Health Organization diagnostic criteria for MDS. AML indicates acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; EVITA, Epigenetics, Vitamin C, and Abnormal Hematopoiesis; MDS, myelodysplastic syndromes; MDS-EB, myelodysplastic syndromes with excess blasts.

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**TABLE 1** Baseline demographic and clinical characteristics of EVITA participants.

| Characteristic | Placebo ($n$ = 54) | Vitamin C ($n$ = 55) |
|---|---|---|
| Follow-up, median (IQR), months | 28.0 (18.1–41.1) | 36.3 (25.7–49.4) |
| Age, median (IQR), years | 75.0 (70.1–79.4) | 72.3 (66.7–78.7) |
| Age, No. (%) | | |
| 18–59 | 1 (2) | 6 (11) |
| 60–74 | 26 (48) | 27 (49) |
| ≥75 | 27 (50) | 22 (40) |
| Male sex, No. (%) | 42 (78) | 36 (65) |
| ECOG performance status score, No. (%) | | |
| 0 or 1 | 52 (96) | 53 (96) |
| 2 or 3 | 2 (4) | 2 (4) |
| Charlson Comorbidity Index score,[a] No. (%) | | |
| 1 or 2 | 3 (6) | 6 (11) |
| 3 or 4 | 21 (39) | 20 (36) |
| ≥5 | 29 (54) | 29 (53) |
| Diagnosis (2016 WHO[18]),[b] No. (%) | | |
| CCUS | 17 (31) | 20 (36) |
| MDS | 22 (41) | 19 (35) |
| CMML | 12 (22) | 12 (22) |
| Other MDS/MPN | 1 (2) | 3 (5) |
| Therapy-related myeloid disorder, No. (%) | 2 (4) | 3 (5) |
| IPSS-R[17] risk category, No. (% of patients with MDS) | | |
| Very low | 13 (59) | 11 (58) |
| Low | 9 (41) | 8 (42) |
| IPSS-M[1] risk category, No. (% of patients with MDS) | | |
| Very low | 9 (41) | 4 (21) |
| Low | 10 (45) | 11 (58) |
| Moderate low | 2 (9) | 2 (11) |
| Moderate high | 0 | 2 (11) |
| High | 1 (5) | 0 |
| CPSS-Mol[23] risk category, No. (% of patients with CMML) | | |
| Low or intermediate 1 | 10 (83) | 7 (58) |
| Intermediate 2 or high | 2 (17) | 5 (42) |
| Time since diagnosis, median (IQR), months | 5.8 (1.7–46.3) | 2.7 (1.4–18.2) |
| Hematological parameters, median (IQR) | | |
| Hemoglobin, g/dL | 11.5 (9.8–12.6) | 11.9 (10.6–12.6) |
| White blood cell count, $\times 10^9$/L | 4.7 (3.7–8.4) | 5.3 (3.2–7.5) |
| Absolute neutrophil count, $\times 10^9$/L | 2.4 (1.3–4.6) | 3.0 (1.4–3.9) |
| Platelet count, $\times 10^9$/L | 134 (103–249) | 150 (99–219) |
| Cytopenias, No. (%) | | |
| 0 or 1 | 22 (41) | 30 (54) |
| 2 | 23 (42) | 18 (33) |
| 3 | 9 (17) | 7 (13) |
| Anemia, No. (%) | 42 (78) | 40 (73) |
| Mean corpuscular volume, median (IQR), fL | 98 (91–106) | 98 (95–104) |
| Red cell distribution width, median (IQR), % | 15 (14–17) | 15 (14–17) |
| Patients receiving erythropoiesis-stimulating agents, No. (%) | 10 (19) | 12 (22) |
| Patients receiving transfusions,[c] No. (%) | 11 (20) | 7 (13) |
| No. of mutations, median (IQR) | 2 (1–4) | 3 (2–4) |
| Patients with >2 mutations, No. (%) | 24 (44) | 33 (60) |
| Patients with variant allele frequency ≥20%, No. (%) | 44 (81) | 45 (82) |
| Vitamin C supplementation, No. (%) | 23 (43) | 24 (44) |
| Vitamin C plasma concentration, No. (%) | | |
| Deficient (<23 μmol/L) | 14 (26) | 11 (20) |
| Inadequate (23–49 μmol/L) | 18 (33) | 19 (35) |
| Adequate (≥50 μmol/L) | 22 (41) | 25 (45) |

Abbreviations: CCUS, clonal cytopenia of undetermined significance; CMML, chronic myelomonocytic leukemia; CPSS-Mol, CMML-specific Prognostic Scoring System–Molecular; ECOG, Eastern Cooperative Oncology Group; EVITA, Epigenetics, Vitamin C, and Abnormal Hematopoiesis; IPSS-M, International Prognostic Scoring System–Molecular; IPSS-R, Revised International Prognostic Scoring System; IQR, interquartile range; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; WHO, World Health Organization.

[a]Not reported for one patient in the placebo group.

[b]In the placebo group, one patient was diagnosed with AML at the baseline bone marrow assessment, and one patient initially diagnosed with CMML-0 was later reclassified as having isolated monocytosis associated with a germline *NF1* mutation. In the vitamin C group, one patient initially diagnosed with CCUS was later reclassified as having idiopathic cytopenia of undetermined significance. These patients were not included in the diagnostic classification shown here.

[c]Defined as any blood product transfusion within 16 weeks before baseline.

shows fold changes in all cytokines and chemokines; subgroup analyses are presented in Supporting Information S1: Figure S7.

We then assessed global DNA methylation levels in CD34$^+$ HSPCs for epigenetic effects of vitamin C. At baseline, patients with *TET2* or *IDH1/2* mutations had a significantly lower 5-hmC/5-mC ratio (mean difference, 0.0029; 95% CI, 0.0018 to 0.0039; FDR-

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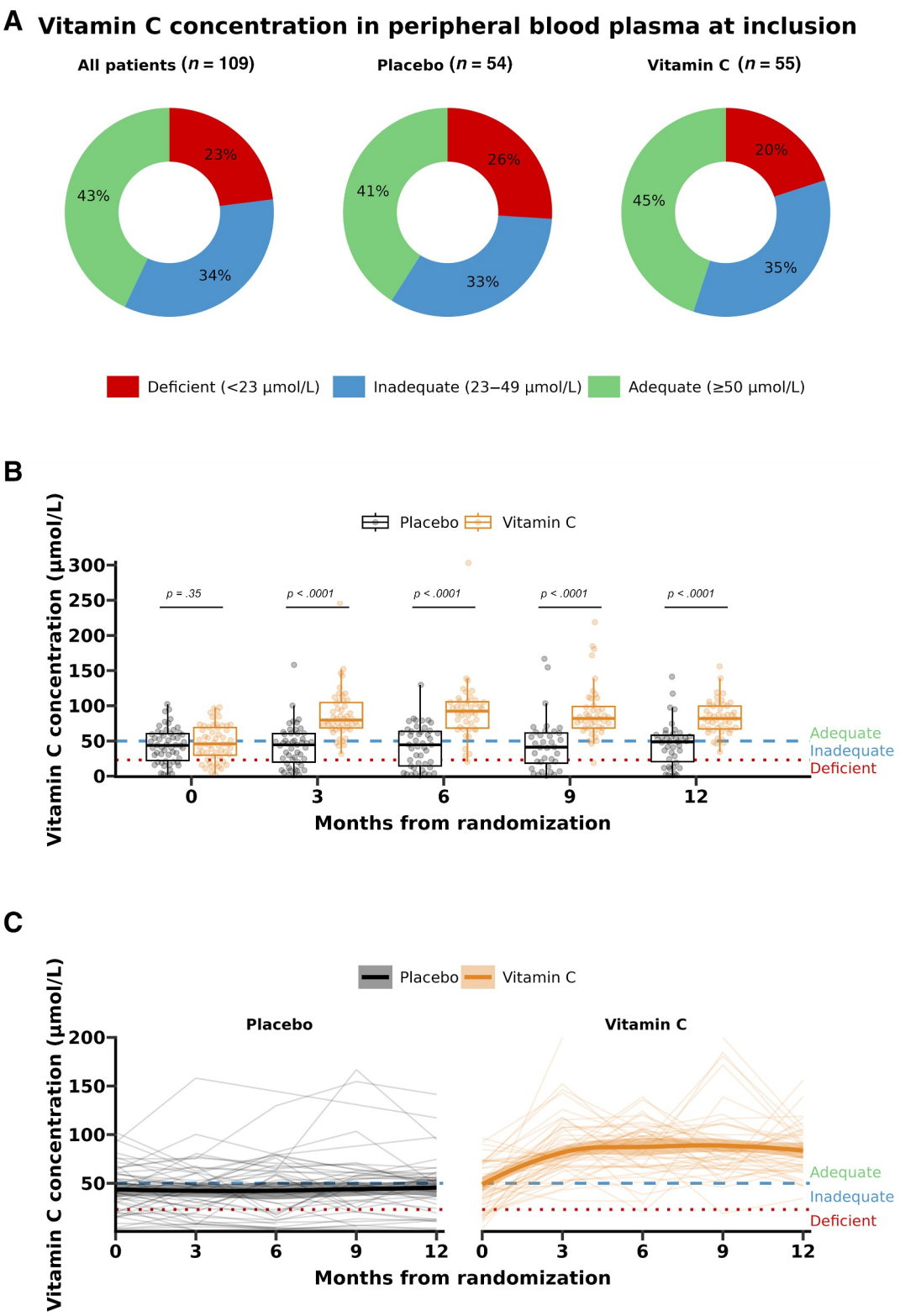


**FIGURE 2** Plasma vitamin C concentrations. Peripheral blood plasma vitamin C levels were measured in all 109 patients at baseline and at 12 months in the 87 patients who completed study treatment (placebo group, $n = 41$; vitamin C group, $n = 46$). (A) Baseline vitamin C status by treatment group. Donut plots show the proportion of patients with deficient (<23 µmol/L), inadequate (23–49 µmol/L), and adequate (≥50 µmol/L) plasma vitamin C concentrations at baseline. (B) Plasma vitamin C concentrations at baseline and during study treatment (months 3, 6, 9, and 12), stratified by treatment group. Boxplots show the interquartile range (IQR), median (horizontal line), and ±1.5× IQR (whiskers); individual data points are overlaid. (C) Longitudinal trajectories of plasma vitamin C concentrations from baseline to 12 months. Thin lines represent individual patients; bold lines indicate locally estimated scatterplot smoothing trends with shaded 95% confidence intervals by treatment group. The red dotted line denotes the lower limit of the normal range (23 µmol/L); the blue dashed line marks the threshold between inadequate (23–49 µmol/L) and adequate (≥50 µmol/L) levels.

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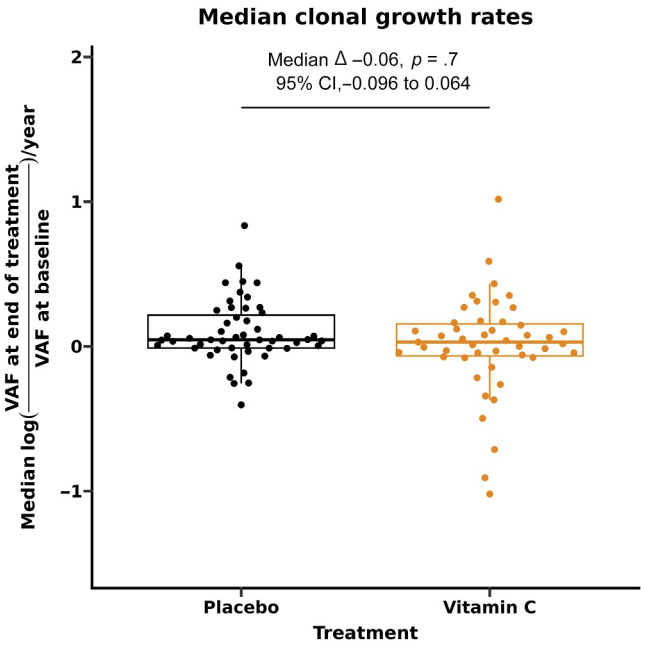


**FIGURE 3** Median clonal growth rates. The primary end point, clonal growth rate, was analyzed in 98 patients (placebo group, $n = 51$; vitamin C group, $n = 47$) after excluding nine patients without follow-up samples and two patients with no detectable mutations at baseline or end of treatment (protocol deviations). End-of-treatment samples were collected at 12 months in the 85 patients who completed treatment (placebo, $n = 41$; vitamin C, $n = 44$) and at 3 months in 13 patients who discontinued study treatment (placebo, $n = 10$; vitamin C, $n = 3$). Next-generation sequencing was performed on paired baseline and end-of-treatment DNA samples, matched by tissue and cell type for each patient. Across the full cohort ($N = 109$), bone marrow $CD34^+$ hematopoietic stem and progenitor cells were used when available ($n = 74$); otherwise, peripheral blood or bone marrow granulocytes ($n = 31$), peripheral blood mononuclear cells ($n = 3$), or bone marrow $CD34^-$ mononuclear cells ($n = 1$) were used. Median clonal growth rates in hematopoietic cells by treatment group are shown. Individual data points represent per-patient median growth rates. Boxes indicate the interquartile range (IQR), horizontal lines indicate the median, and whiskers extend to ± 1.5× IQR. VAF indicates variant allele frequency.

corrected $p < .0001$; Supporting Information S1: Figure S8), whereas neither global 5-mC levels nor 5-hmC/5-mC ratios differed by other baseline characteristics or correlated with vitamin C concentration (Supporting Information S1: Figures S8–S10; all $R^2 < 0.03$; all $p > .05$).

No between-group differences were observed in the change from baseline to end of treatment in global 5-mC levels (interaction estimate, −0.0004; 95% CI, −0.0014 to 0.0005; $p = .36$) or in 5-hmC/5-mC ratios (−0.0001; 95% CI, −0.0006 to 0.0004; $p = .77$) (Supporting Information S1: Figure S11). In subgroup analyses, patients with CCUS treated with vitamin C showed a greater reduction in global 5-mC levels compared to placebo (Supporting Information S1: Figure S12), whereas no clear differences were observed in other subgroups (Supporting Information S1: Figures S12–S14).

## Clinical outcomes

To assess clinical outcomes, we examined progression to higher-risk myeloid malignancies defined as MDS or MDS/MPN (except for CMML) with bone marrow blasts of ≥5% or blood blasts of ≥2%, CMML-2, or AML, according to the 2016 WHO classification.[18] From randomization to end of study, the median follow-up in the ITT population was 33.6 months (IQR, 21.4–48.3 months), with 14 recorded progression events, nine in the placebo group (AML, $n = 7$; CMML-2, $n = 1$; MDS with excess blasts [MDS-EB] 1, $n = 1$) and five in the vitamin C group (AML, $n = 3$; MDS-EB-1 or -2, $n = 2$). A competing risks regression, with death as a competing event, estimated a lower risk of progression in the vitamin C group, although this was not significant (hazard ratio [HR], 0.51; 95% CI, 0.17 to 1.51; $p = .22$; Supporting Information S1: Figure S15).

Results on hematological improvement and hematological progression are provided in Supporting Information S1 (p 34), with no differences observed between groups.

## Safety

During the safety-monitoring period, total treatment exposure was 577.3 patient-months in the placebo group and 592.9 patient-months in the vitamin C group. AEs were reported in 32 of 53 patients (60%) in the placebo group and 24 of 55 patients (44%) in the vitamin C group, with a total of 82 and 54 events, respectively (Table 2). SAEs were also more frequent in the placebo group, with 66 SAEs in 30 patients (57%) compared to 39 SAEs in 18 patients (33%) in the vitamin C group (Table 2). AEs and SAEs occurring in more than one patient in either treatment group are summarized in Table 3.

Notably, anemia (eight of 53 [15%] vs. four of 55 [7%]), pneumonia (eight of 53 [15%] vs. one of 55 [2%]), acute aseptic arthritis (three of 53 [6%] vs. 0), and internal bleeding (three of 53 [6%] vs. 0) occurred more frequently in the placebo group than in the vitamin C group. Conversely, gastrointestinal AEs were less frequent in the placebo group than in the vitamin C group, including diarrhea (one of 53 [2%] vs. three of 55 [5%]), esophagitis (0 vs. three of 55 [5%]), and gastrointestinal infections (0 vs. two of 55 [4%]).

To account for differences in treatment duration, exploratory exposure-adjusted incidence rates (EAIRs) were also calculated. The EAIR of AEs was 14.2 (95% CI, 11.3 to 17.6) per 100 patient-months in the placebo group and 9.1 (95% CI, 6.8 to 11.9) in the vitamin C group. For SAEs, the EAIRs were 11.4 (95% CI, 8.8 to 14.5) and 6.6 (95% CI, 4.7 to 9.0), respectively (Table 2).

Higher doses of vitamin C may increase oxalate formation and accelerate kidney stone formation. One case of kidney stones requiring intervention occurred during treatment in the vitamin C group, in a patient with kidney stones more than a year earlier.

During study treatment, two deaths occurred in the placebo group (4%), both disease related; no deaths were reported in the vitamin C group (Table 2).

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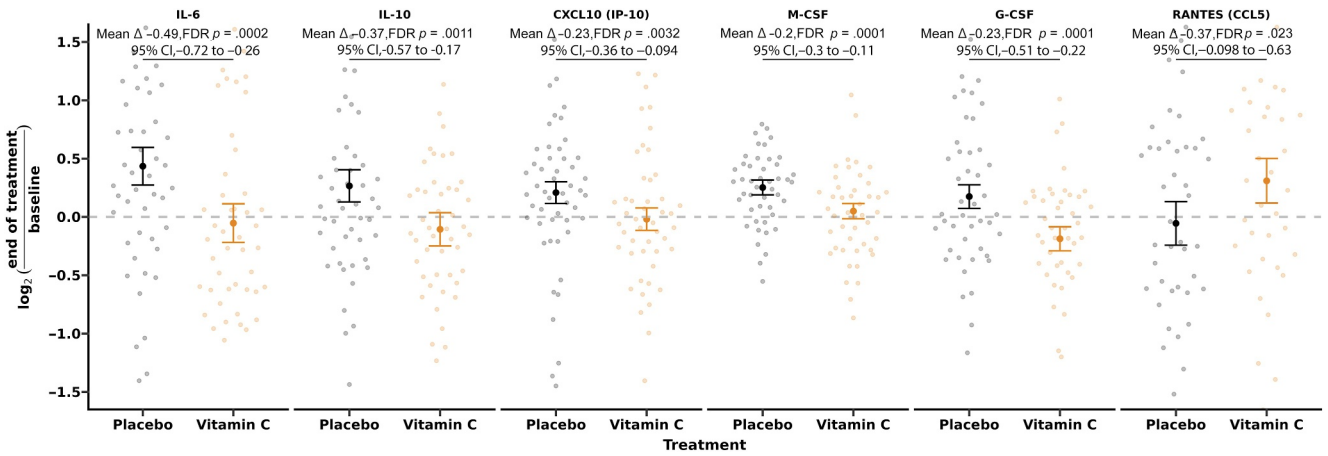


**FIGURE 4** Cytokine and chemokine levels. Cytokine and chemokine levels were analyzed in 98 patients (placebo, $n = 50$; vitamin C, $n = 48$), excluding 10 patients who discontinued treatment without follow-up plasma samples and one patient without a baseline plasma sample for cytokine analysis. End-of-treatment values were from 12 months in the 85 patients who completed treatment (placebo, $n = 41$; vitamin C, $n = 44$) and from 3 months in the remaining 13 (placebo, $n = 9$; vitamin C, $n = 4$). Of the 19 cytokines and chemokines analyzed, six showed significantly different changes in plasma concentration from baseline to end of treatment between the vitamin C and placebo groups after adjustment for multiple testing via the Benjamini–Hochberg FDR method. $Log_2$ fold changes ($log_2$[FC]s) for these six analytes are shown. Individual patient values are shown as dots, with means and 95% CI error bars indicated. The scale was limited to $\pm 1.5$ $log_2$[FC] to improve visualization of dispersion; all data points from each of the 19 total analytes are shown in Supporting Information S1: Figure S6. The following analytes increased more in the placebo group than in the vitamin C group: IL-6 (median increase of 978.7 μg/mL [FC = 1.35] vs. median decrease of 305.2 μg/mL [FC = 0.96]; FDR-corrected $p = .0002$), IL-10 (48.3 μg/mL increase [FC = 1.2] vs. 48.4 μg/mL decrease [FC = 0.93]; FDR-corrected $p = .0011$), CXCL10 (97.4 μg/mL increase [FC = 1.16] vs. 26.4 μg/mL decrease [FC = 0.99]; FDR-corrected $p = .0032$), M-CSF (1.96 μg/mL increase [FC = 1.19] vs. 0.43 μg/mL increase [FC = 1.03]; FDR-corrected $p = .0001$), and G-CSF (0.36 μg/mL increase [FC = 1.13] vs. 0.94 μg/mL decrease [FC = 0.88]; FDR-corrected $p < .0001$). In contrast, RANTES/CCL5 decreased more in the placebo group than in the vitamin C group (47.1 μg/mL decrease [FC = 0.96] vs. 337.4 μg/mL increase [FC = 1.2]; FDR-corrected $p = .023$). CXCL10 indicates C-X-C motif chemokine ligand 10; FDR, false discovery rate; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; RANTES/CCL5, regulated on activation, normal T cell expressed and secreted/C-C motif chemokine ligand 5.

**TABLE 2** Overview of adverse events and serious adverse events.

| | Placebo ($n = 53$) | | | | Vitamin C ($n = 55$) | | | |
|---|---|---|---|---|---|---|---|---|
| | Patients, No. (%) | | Events, No. | | Patients, No. (%) | | Events, No. | |
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any adverse event | 32 (60) | 28 (53) | 82 | 56 | 24 (44) | 18 (33) | 54 | 39 |
| Adverse events leading to withdrawal | 1 (2) | 1 (2) | 1 | 1 | 3 (5) | 0 | 3 | 0 |
| Serious adverse events | 30 (57) | — | 66 | — | 18 (33) | — | 39 | — |
| Deaths | 2 (4) | NA | 2 | NA | 0 | NA | 0 | NA |
| Incidence rate per 100 patient-months | NA | NA | 14.2 (95% CI, 11.3–17.6) | 11.4 (95% CI, 8.8–14.5) | NA | NA | 9.1 (95% CI, 6.8–11.9) | 6.6 (95% CI, 4.7–9.0) |

*Note:* The safety analysis included 53 patients in the placebo group and 55 patients in the vitamin C group. One patient in the placebo group, who did not receive the allocated intervention and was lost to follow-up soon after randomization because of relocation, was excluded after randomization. This table is an overview of the total number of events and number (%) of affected patients by severity (any grade and grade ≥3), including events leading to withdrawal, SAEs, and deaths. Exploratory exposure-adjusted incidence rates per 100 patient-months were calculated to account for differences in treatment duration between groups.

Abbreviation: NA, not applicable.

## Exploratory analyses

Overall survival was analyzed as a post hoc exploratory end point. At a median follow-up of 33.6 months in the ITT population, 35 deaths were recorded from randomization to end of study, including 24 in the placebo group and 11 in the vitamin C group. The median overall survival was 42.2 months (95% CI, 30.3 months to not estimable) in the placebo group, whereas it was not reached in the

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**TABLE 3** Individual adverse events and serious adverse events reported in more than one patient.

| | Placebo ($n$ = 53) | | | | | | Vitamin C ($n$ = 55) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients, No. (%) | | | Events, No. | | | Patients, No. (%) | | | Events, No. | | |
| Adverse event in >1 patient | Any grade | Grade ≥3 | Serious | Any grade | Grade ≥3 | Serious | Any grade | Grade ≥3 | Serious | Any grade | Grade ≥3 | Serious |
| Neutropenia | NA | 8 (15) | 8 (15) | NA | 8 | 8 | NA | 7 (13) | 7 (13) | NA | 7 | 7 |
| Anemia | NA | 8 (15) | 8 (15) | NA | 14 | 14 | NA | 4 (7) | 4 (7) | NA | 5 | 5 |
| Pneumonia | 8 (15) | 5 (9) | 5 (9) | 8 | 5 | 5 | 1 (2) | 1 (2) | 1 (2) | 1 | 1 | 1 |
| Thrombocytopenia | NA | 3 (6) | 3 (6) | NA | 3 | 3 | NA | 4 (7) | 4 (7) | NA | 4 | 4 |
| Bacterial infection, other | 4 (8) | 2 (4) | 2 (4) | 4 | 2 | 2 | 2 (4) | 1 (2) | 1 (2) | 2 | 1 | 1 |
| Nonhematological malignant tumors | 4 (8) | 3 (6) | 4 (8) | 4 | 3 | 4 | 1 (2) | 0 | 1 (2) | 1 | 0 | 1 |
| Urinary tract infection | 2 (4) | 1 (2) | 1 (2) | 2 | 1 | 1 | 3 (5) | 0 | 0 | 4 | 0 | 0 |
| Diarrhea | 1 (2) | 1 (2) | 1 (2) | 1 | 1 | 1 | 3 (5) | 1 (2) | 1 (2) | 3 | 1 | 1 |
| Acute aseptic arthritis | 3 (6) | 3 (6) | 3 (6) | 8 | 6 | 8 | 0 | 0 | 0 | 0 | 0 | 0 |
| Internal bleeding | 3 (6) | 2 (4) | 3 (6) | 4 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| Aortic stenosis | 1 (2) | 1 (2) | 1 (2) | 1 | 1 | 1 | 2 (4) | 2 (4) | 2 (4) | 2 | 2 | 2 |
| Esophagitis | 0 | 0 | 0 | 0 | 0 | 0 | 3 (5) | 3 (5) | 3 (5) | 3 | 3 | 3 |
| Transient ischemic attack | 2 (4) | 0 | 2 (4) | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastritis | 1 (2) | 0 | 1 (2) | 1 | 0 | 1 | 1 (2) | 1 (2) | 1 (2) | 1 | 1 | 1 |
| Nausea | 1 (2) | 0 | 0 | 1 | 0 | 0 | 1 (2) | 0 | 0 | 1 | 0 | 0 |
| Stroke | 1 (2) | 0 | 1 (2) | 1 | 0 | 1 | 1 (2) | 1 (2) | 1 (2) | 1 | 1 | 1 |
| Iron deficiency | 1 (2) | 1 (2) | 0 | 1 | 1 | 0 | 1 (2) | 1 (2) | 0 | 1 | 1 | 0 |
| Unintentional weight loss | 1 (2) | 1 (2) | 1 (2) | 1 | 1 | 1 | 1 (2) | 0 | 1 (2) | 1 | 0 | 1 |
| Infectious colitis, enteritis, and gastroenteritis | 0 | 0 | 0 | 0 | 0 | 0 | 2 (4) | 1 (2) | 1 (2) | 2 | 1 | 1 |

*Note:* The safety analysis included 53 patients in the placebo group and 55 patients in the vitamin C group. One patient in the placebo group, who did not receive the allocated intervention and was lost to follow-up soon after randomization because of relocation, was excluded after randomization. Individual adverse events reported in more than one patient in either treatment group are shown by severity (any grade and grade ≥3) and seriousness.
Abbreviation: NA, not applicable.

vitamin C group (HR, 0.35; 95% CI, 0.17 to 0.71; $p$ = .0025) (Figure 5).

Causes of death are detailed in Supporting Information S1: Table S6. Bacterial infection was the leading cause, attributed to 14 of 24 (58%) and five of 11 (45%) deaths in the placebo and vitamin C groups, respectively, followed by AML (three of 24 [13%] vs. one of 11 [9%]). Disease-related deaths—defined as death due to infection, bleeding, disease progression, or adult failure to thrive, with myeloid malignancy as the most likely underlying cause—accounted for 14 of 24 (58%) in the placebo group and five of 11 (45%) in the vitamin C group.

To assess potential confounding, we performed a multivariable analysis adjusting for age, sex, baseline hemoglobin, and CCUS diagnosis. Randomization to vitamin C remained independently associated with significantly lower all-cause mortality (adjusted HR, 0.42; 95% CI, 0.20 to 0.88; $p$ = .021; Supporting Information S1: Figure S16).

Increased age (above the mean) appeared to attenuate the association between vitamin C treatment and longer overall survival (HR, 1.13 per decade; 95% CI, 1.02 to 1.26 per decade; $p$ = .022; Supporting Information S1: Figure S17A), whereas none of the other assessed variables, including baseline vitamin C concentration, showed evidence of effect modification (all $p$ > .15; Supporting Information S1: Figure S17B–E). A sensitivity analysis of overall survival based on the per-protocol population is shown in Supporting Information S1: Figure S18.

Given that this interventional trial evaluated a dietary vitamin present in all participants regardless of treatment assignment, we assessed the relationship between plasma vitamin C concentrations and overall survival across the entire cohort. Median plasma vitamin C concentration for each patient during the treatment period was evaluated in relation to overall survival after adjustment for age, sex, baseline hemoglobin, and CCUS diagnosis. Corresponding

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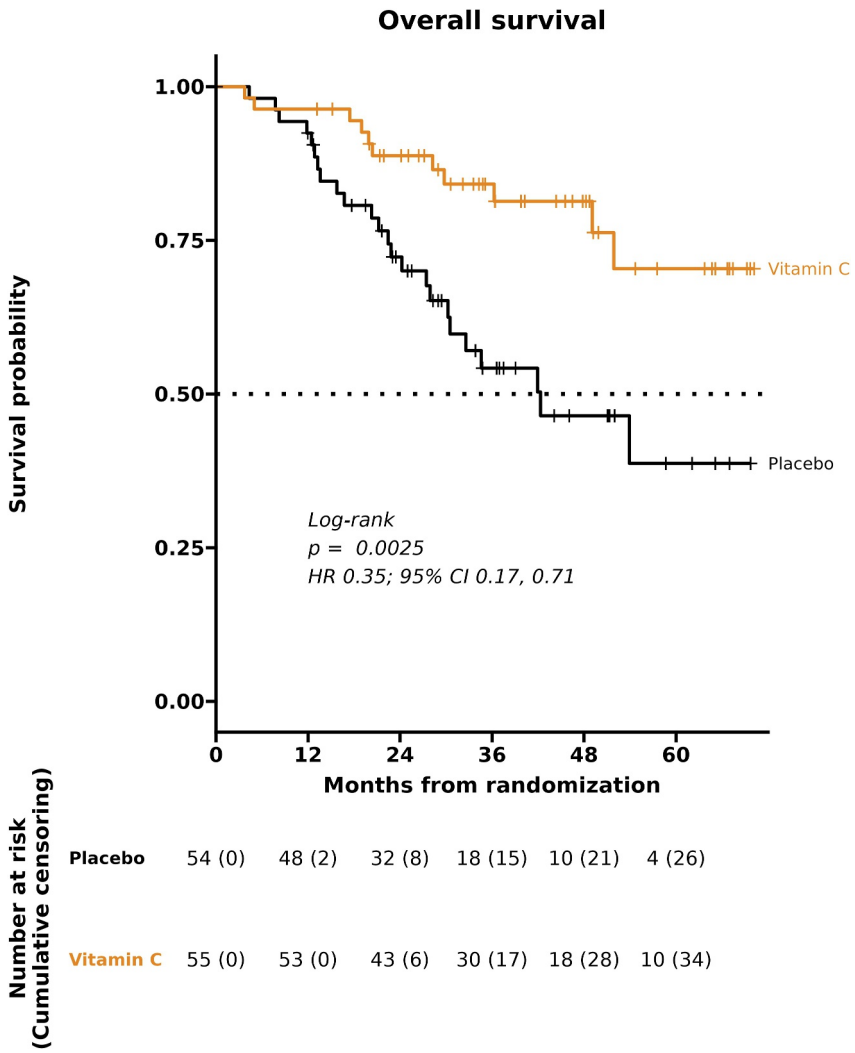


**FIGURE 5** Overall survival. Kaplan–Meier curves showing overall survival by treatment group in the intention-to-treat population. The HR with 95% CI was estimated via an unadjusted Cox proportional hazards model. The log-rank *p* value is shown. Numbers at risk and cumulative censoring counts are displayed below the x-axis. HR indicates hazard ratio.

model-based 5-year survival estimates are shown in Supporting Information S1: Figure S19. The findings suggest a nonlinear concentration–survival relationship, with predicted 5-year survival probability increasing substantially with relatively small increases in plasma vitamin C concentration at lower concentrations, whereas further increases at higher concentrations were associated with more modest gains, consistent with an association between higher plasma vitamin C concentration and longer overall survival (HR, 0.45; 95% CI, 0.21 to 0.95).

## DISCUSSION

Management of patients with CCUS or lower risk myeloid malignancies remains a clinical challenge in the absence of established interception strategies. Although the risk of progression to advanced disease is low, many patients experience significant symptoms related to cytopenias.

Vitamin C is best known as a cofactor for prolyl hydroxylation in collagen synthesis, and was originally discovered via its role in preventing scurvy. Notably, the incidence of scurvy has increased in recent years, including a more than 3-fold rise among pediatric patients in the United States between 2016 and 2020,[25] which suggests that vitamin C deficiency may be more prevalent than generally appreciated.

In this exploratory phase 2 double-blind RCT of adults with CCUS or lower risk myeloid malignancies, a substantial proportion of patients had deficient or inadequate vitamin C levels at baseline, consistent with previous reports,[15, 16] and these deficiencies were corrected with oral administration of 1000 mg vitamin C daily. There was no difference in the primary end point, clonal growth rate, between patients treated with oral vitamin C for 12 months and those receiving placebo. Vitamin C was generally safe and well tolerated, with fewer AEs and SAEs than in the placebo group.

Although no effect was observed for the primary end point, between-group differences emerged in secondary and exploratory

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outcomes. Among the latter, overall survival was significantly longer in the vitamin C group compared to placebo. Although the study was neither powered nor designed to assess survival outcomes, the signal remained consistent across multivariable models adjusting for baseline imbalances suggestive of a higher risk placebo population, supporting the internal validity of the finding. The shorter overall survival in the placebo group compared to other studies or prognostic estimates[1] may in part reflect the inclusion of both newly and previously diagnosed patients, which makes survival appear shorter when measured from randomization rather than from diagnosis. Importantly, the estimated median age at death in the placebo group (75 years at baseline plus a median survival of 42.2 months: ~78.5 years) closely matches the life expectancy for Danish men (79.9 years),[26] which indicates that survival in the placebo group was well aligned with the background population and disease context. Taken together, these observations do not suggest that the placebo group was characterized by a higher than expected baseline disease burden or risk profile.

Indications of biological activity of vitamin C emerged from the analysis of cytokine levels. The direction of changes in cytokine and chemokine levels in the vitamin C group during treatment—attenuated increases or even decreases in IL-6, IL-10, CXCL10, M-CSF, and G-CSF, and a greater increase in RANTES/CCL5 compared to placebo—is consistent with our previous observations of a cytokine profile characteristic of lower risk rather than higher risk myeloid disease and of healthy controls compared to patients with myeloid disease.[27] In support of this, increased proinflammatory cytokine secretion, particularly IL-6, has been shown in mouse models to be critical for the expansion of *TET2*- and *DNMT3A*-mutated preleukemic HSCs,[28, 29] and human in vitro studies have demonstrated that vitamin C can reduce levels of IL-6 and other proinflammatory cytokines after antigen stimulation.[30–33] These findings support a potential modulatory effect of vitamin C on inflammatory pathways implicated in clonal expansion and disease progression. Whether the observed cytokine changes reflect epigenetic alterations in immune cell subsets is the subject of ongoing investigation.

As previously reported,[16] we observed a lower global 5-hmC/5-mC ratio in HSPCs at baseline in patients with *TET2* or *IDH1/2* mutations. However, no overall treatment-related differences were seen in global 5-mC levels or 5-hmC/5-mC ratios.

To our knowledge, only one other study[34] has investigated vitamin C treatment in patients with CCUS or lower risk MDS. This single-arm phase 2 study tested high-dose iv vitamin C (1 g/kg thrice weekly for 12 weeks) in patients with *TET2*-mutated CCUS ($n = 10$). Consistent with our findings, no hematological responses were observed at 20 weeks, and *TET2*-mutated VAFs remained largely stable at 20 and 52 weeks.[34]

A second, nonrandomized study[35] investigated the epigenetic effects of oral vitamin C (1000 mg/day for 12 months) in whole blood in a family with a germline heterozygous *TET2* loss-of-function mutation, including three unaffected mutation carriers and three mutation-negative relatives. At baseline, unaffected mutation carriers exhibited a higher proportion of hypermethylated CpGs in enhancer regions. This hypermethylation was reversed after 12 months of treatment.[35]

Limitations of this study include the relatively small sample size and lack of a formal sample size calculation, which may have limited power to detect modest differences in the primary end point and raises the possibility of a type II error. Treatment was limited to 12 months, after which undocumented posttreatment vitamin C exposure may have introduced informal crossover, which potentially influenced long-term outcomes. Future trials should extend treatment until the end of the study to ensure consistency.

Furthermore, accumulating evidence suggests that clonal dynamics over the course of 1 year in patients with CCUS or lower risk myeloid malignancies are relatively stable and gene dependent, and have a complex relationship with clinical outcomes. In this trial, median proportional increases in VAF were 4.6% per year in the placebo group and 3.03% in the vitamin C group, comparable to recent prospective studies reporting mean annual increases of approximately 4% overall.[36, 37] Therefore, clonal growth rate is not a suitable surrogate end point for treatment efficacy in this patient population. At the time of study design, however, the presence of mutations and clone size were widely considered to be closely linked to clinical outcomes, which informed the selection of clonal growth rate as the primary end point.[38, 39]

We used an oral dosing strategy to target epigenetic dysregulation via the cofactor role of vitamin C for TET2, rather than the potential cytotoxic effects associated with high-dose iv administration. On the basis of pharmacokinetic studies,[40] we hypothesized that a daily oral dose of 1000 mg would achieve plasma saturation (~70–80 μmol/L) in patients and be sufficient to enhance epigenetic activity, as demonstrated in mouse models of leukemia driven by heterozygous *Tet2* mutations.[14, 41] While iv administration may exert greater effects, our findings support the biological activity of oral vitamin C at this dose and its potential as a safe and accessible approach to disease interception.

In conclusion, EVITA is the first RCT to evaluate vitamin C supplementation in patients with CCUS or lower risk myeloid malignancies, an inexpensive and essentially nontoxic intervention suitable for interception strategies. Although no difference was observed in the primary end point, the trial showed biological activity of oral vitamin C, as reflected by changes in cytokine levels, alongside signals of potential clinical relevance in both prespecified and exploratory outcomes. These hypothesis-generating findings provide a rationale for further evaluation in a phase 3 trial.

## AUTHOR CONTRIBUTIONS

**Stine Ulrik Mikkelsen:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing–original draft, and writing–review and editing. **Ali Al-Mousawi:** Formal analysis and writing–review and editing. **Amalie Bach Puglisi:** Data curation, investigation, resources, and writing–review and editing. **Anders Pommer Vallentin:** Data curation, investigation, resources, and

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## CONFLICT OF INTEREST STATEMENT

Jakob Werner Hansen reports professional activities for GlaxoSmithKline and AbbVie. Casey Lee O'Connell reports consulting for Geron and Taiho Oncology. Peter Jones is a paid consultant/scientific advisory board member for Zymo Research. Kirsten Grønbæk reports grants from Janssen Pharmaceuticals and Medac. The other authors declare no conflicts of interest.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are partially available in Supplementary Material. Additional raw data can be made available from the corresponding author on reasonable request, subject to successful anonymization. Because of patient confidentiality and ethical restrictions, individual participant data are not publicly available. Analysis code can be accessed at https://github.com/vari-bbc/EVITA_Analysis.

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