ICH E3 Synopsis

Randomized, Multi-centre, Phase II Trial to compare the Event-Free Survival of Clofarabine / Ara-C (ClAraC) or of FLAMSA Treatment in Patients with High Risk AML or Advanced MDS scheduled for Allogeneic Stem Cell Transplantation

Investigational product: ClAraC (clofarabine / ara-C) regimen

Indication: Patients with high risk acute myeloid leukemia (AML) or advanced myelodysplastic syndrome (MDS) scheduled for allogeneic stem cell transplantation (SCT)

EudraCT number: 2010-021944-17

Study initiation date (first patient enrolled): 17.08.2011
Study completion date (last patient completed): 15.05.2017

Protocol code number: ClAraC-SCT-01
Development phase of study: II

Sponsor of the clinical trial:

Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover, Germany

Coordinating investigator:

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Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation
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This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents

Version / Date: 1.1/ 14.05.2018

2 Synopsis

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Clofarabine 1mg/ml concentrate for solution for infusion (Evoltra® 1 mg/ml, study specific labelled) Cytarabine, all approved medicinal products in Germany Fludarabine, all approved medicinal products in Germany Amsacrine, all approved medicinal products in Germany	Volume:	
Name of Active Ingredient: Clofarabine Cytarabine Fludarabine Amsacrine	Page:	

Title of study:
Randomized, Multi-centre, Phase II Trial to compare the Event-Free Survival of Clofarabine / Ara-C (ClAraC) or of FLAMSA Treatment in Patients with High Risk AML or Advanced MDS scheduled for Allogeneic Stem Cell Transplantation

EudraCT number: 2010-021944-17
Protocol code number: ClAraC-SCT-01

Information about study protocol versions:

Protocol version 2.0, Date: 21.04.2011

Subsequent substantial amendments:
Protocol version 3.0, Date: 22.05.2012
Protocol version 4.0, Date: 17.09.2012
Protocol version 9.0, Date: 28.10.2014

Study coordination:
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Publication (reference): Puplication in preparation

Studied period (years):	**Phase of development:** Phase II
2011 - 2017 date of first enrolment: FPFV 17.08.2011 date of last completed: LPLV 15.05.2017 Temporary halt(s) and early termination: --	

Objectives:

Primary Objective:

To demonstrate that event-free survival is improved by using ClAraC instead of the FLAMSA regimen.

Secondary Objectives:

1. Investigation of (a) overall and (b) relapse-free survival
2. Investigation of morbidity and mortality after allogeneic SCT with focus on cardiac toxicity
3. Investigation of rate of engraftment
4. Investigation of kinetics of chimerism after allogeneic SCT

Assessment of safety:

To evaluate the toxicity and safety of ClAraC and in comparison to FLAMSA in the setting of allogeneic SCT in patients with high risk AML or advanced MDS.

Methodology:

This is a prospective, multi-centre, open-label, two-armed, parallel-group, randomized phase II study.

Three centers (Hannover, Leipzig, Jena) recruited a total of 62 patients.

Randomization was stratified for centre and remission state:

- stratum 1: AML with complete remission (blasts ≤ 5%)
- stratum 2: AML without complete remission (blasts > 5%) or advanced MDS

A minimum follow up time of 18 months was planned.

This trial was planned as an open-label study. Blinding of patients and treating physicians was not possible, because of different treatment schedules in the two treatment arms.

Due to the open nature of the trial, the randomization was performed centrally (via facsimile) by the Institute of Biostatistics, Hannover Medical School. Randomization was stratified by centre and remission state with variable block length of 2 and 4.

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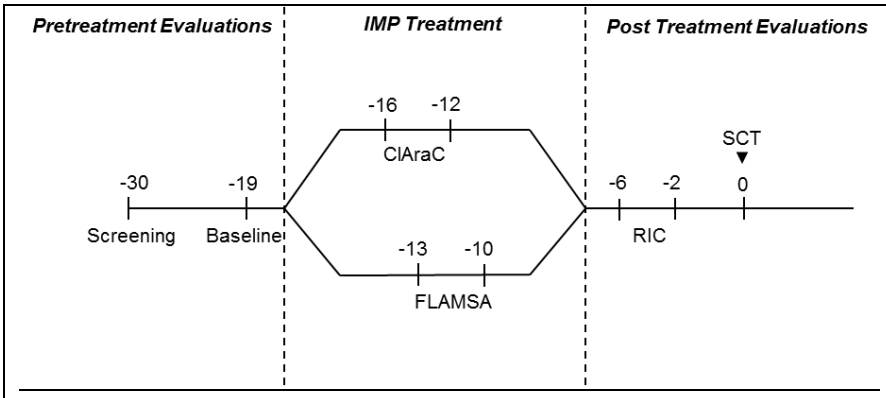
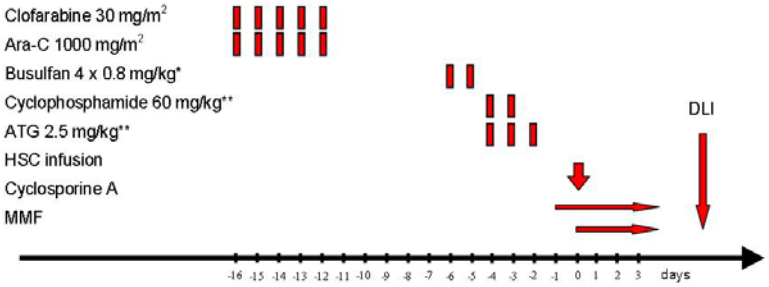
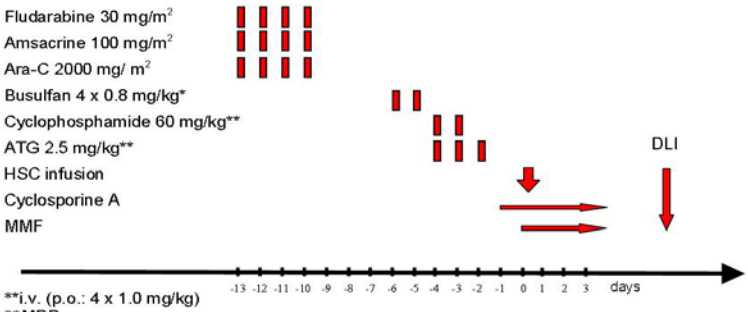


Flowchart ClAraC arm



*i.v. (p.o.: 4 x 1.0 mg/kg)
**MRD:
Cyclophosphamid 40 mg/kg
ATG 1.5 mg/kg

Flowchart FLAMSA arm



**i.v. (p.o.: 4 x 1.0 mg/kg)
**MRD:
Cyclophosphamid 40 mg/kg
ATG 1.5 mg/kg

There were no changes in the conduct of the study with relevance to the assessment of the trial.

Number of patients (planned and analysed):

Planned:

To be allocated to trial: n=60
To be analysed: n=60

Analysed:

Included: n=62,

Randomised: total n=60 (2 patients did not fulfil criteria for inclusion/exclusion),

ClAraC group n=30, FLAMSA group n=30

According to intention-to-treat (ITT) principle, all 60 randomised patients were included in the primary analysis population (ITT-population).

Diagnosis and criteria for inclusion/exclusion:

Patients with high risk acute myeloid leukemia (AML) or advanced myelodysplastic syndrome (MDS) scheduled for allogeneic stem cell transplantation (SCT) were included in this clinical trial.

Inclusion Criteria

1. Signed written informed consent
2. Age ≥ 18 at the day of inclusion
3. Patients with high risk AML or advanced MDS (IPSS score ≥ intermediate 2) scheduled for an allogeneic SCT from HLA-matched related or unrelated donor
4. Amount of blasts < 60% (bone marrow)
5. Patients fulfilling at least one of the following risk factors:
   • Contraindication for conventional conditioning therapy
   • Relapsed or refractory to induction therapy
6. Adequate renal, hepatic and cardiac functions as indicated by the following values:
   • Serum creatinine ≤ 1.0 mg/dL; if serum creatinine > 1.0 mg/dL, then the estimated glomerular filtration rate* (GFR) must be >60 mL/min/1.73 m2
   • Serum bilirubin ≤ 1.5 × upper limit of normal (ULN)
   • Aspartate transaminase (AST) / alanine transaminase (ALT) ≤ 2.5 × ULN
   • Alkaline phosphatase ≤ 5 × ULN
   • Left ventricular ejection fraction ≥ 50 %
7. Capable of understanding the investigational nature, potential risks and benefits of the study, and able to provide valid informed consent
8. Female patients of childbearing potential must have a negative serum pregnancy test at the day of inclusion
9. Female patients must meet one of the following criteria:
   • For female patients ≥50 years of age at the day of inclusion: Menopause since at least 1 year
   • Female patients < 50 years of age at the day of inclusion who meet all of the following criteria:
      − menopause since at least 1 year
      − serum FSH levels > 40 mIU/mL
      − serum estrogen levels < 30 pg/mL or negative estrogen test
   • 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral ovariectomy with or without hysterectomy
   • Correct use of two reliable contraception methods from the time of screening and during the study for a minimum of 90 days after the last administration of study medication. This includes every combination of a hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring) or of an intrauterine device (IUD) with a barrier method (diaphragm, cervical cap, Lea contraceptive, femidom or condom) or with a spermicide. In case the patient takes hormone preparations for suppression of menstruation during the period of aplasia, a suitable and effective method of contraception has to be discussed with the investigator and used by the patient
   • General sexual abstinence from the time of screening, during the study until a minimum of 90 days after the last administration of study medication
   • Having only female sexual partners
   • Monogamous relationship with sterile partner
10. Male patients must meet one of the following criteria:
    • 6 weeks after surgical sterilization by vasectomy
    • Correct use of two reliable contraception methods from the time of screening and during the study for a minimum of 90 days after the last administration of study medication. This includes every combination of a hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring) or of an intrauterine device (IUD) with a barrier method (diaphragm, cervical cap, Lea contraceptive, femidom or condom) or with a spermicide.

• General sexual abstinence from the time of screening, during the study until a minimum of 90 days after the last administration of study medication
• Having only male sexual partners
• Monogamous relationship with sterile partner

Exclusion criteria

1. Patients with acute promyelocytic leukemia with t(15;17)
2. Current concomitant chemotherapy, radiation therapy, or immunotherapy other than as specified in the protocol
3. Any anticancer therapy within 2 weeks before study entry with the exception of hydroxyurea. The patient must have recovered from all acute toxicities from any previous therapy
4. Current participation in any other clinical trial and/or participation in another clinical trial within 30 days before the trial begins (Exception: Parallel participation in the follow-up period of any other trial at least 30 days after end of intervention)
5. Have any other severe concurrent disease, or have a history of serious organ dysfunction or disease involving the heart (heart insufficiency ≥ NYHA II), kidney (serum creatinine > 1.5 x normal serum level), liver (bilirubin > 1.5 x normal serum level, AST /ALT > 2.5 x normal serum level, AP > 5 x normal serum level), or other organ system that may place the patient at undue risk to undergo treatment
6. Patients with a systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment)
7. Human immunodeficiency virus (HIV) positivity
8. Pregnant or lactating patients
9. Any significant concurrent disease, illness, or psychiatric disorder that would compromise patient safety or compliance, interfere with consent, study participation, follow up, or interpretation of study results
10. Have had a diagnosis of another malignancy, unless the patient has been disease-free for at least 3 years following the completion of curative intent therapy, with the following exceptions:
    - Patients with treated non-melanoma skin cancer, in situ carcinoma, or cervical intraepithelial neoplasia, regardless of the disease-free duration, are eligible for this study if definitive treatment for the condition has been completed
    - Patients with organ-confined prostate cancer with no evidence of recurrent or progressive disease based on prostate-specific antigen (PSA) values are also eligible for this study if hormonal therapy has been initiated or a radical prostatectomy has been performed

Test product, dose and mode of administration, batch number:

ClAraC regimen

Clofarabine 1 mg/ml concentrate for solution for infusion (Evoltra® 1 mg/ml, study specific labelled);
30 mg/m², i.v., one hour infusion

Cytarabine, all approved medicinal products in Germany;
1000 mg/m², i.v., two hour infusion three hours after clofarabine

Clofarabine batch numbers:
008225, K0003 (1), K0004 (1), K1002H04, K1003H13

Cytarabine batch numbers:
Ara cell®: 4N296E5, 4D276F4, 4C269D4, 3L261N3, 3J252L3, 3H247I3, 3E241H3, 2M226D3, 2K221M2, 2D205G2, 1N196E2, 1I184J1, 1F177H1, 0N165C1

Duration of treatment:

The conditioning regimen will be one of the following due to randomisation:
4 days FLAMSA regimen:
Fludarabine: days – 13 to - 10
Amsacrine: days – 13 to - 10
Cytarabine: days – 13 to - 10

5 days ClAraC regimen:
Clofarabine: days – 16 to – 12
Cytarabine: days – 16 to – 12

Reference therapy, dose and mode of administration, batch number:

FLAMSA regimen

Fludarabine, all approved medicinal products in Germany;

30 mg/m², i.v., one hour infusion

Amsacrine, all approved medicinal products in Germany;
100 mg/m², i.v., one hour infusion

Cytarabine, all approved medicinal products in Germany;
2000 mg/m², i.v., two hour infusion three hours after fludarabine

Fludarabine batch numbers:

Fludarabinphosphat-GRY®: 14G09LA, 14C31KE, 14A21KA, 13I19MB, 13A09LC, 12G11KG, 12E15LJ, 11K21KI, 09D22MC

Fludarabin HEXAL®: 12020813

Fludarabinmedac: H110332A, F130494A, A140232B, A130031A, A110005B

Fludarabin-Actavis: AU12006L

Amsacrine batch numbers:

Amsidyl®: 1401038, 1311043 1308007, 1303011, 1301049, 1211003, 1209015, 1109031, 1106037, 1105007, 1104034

Cytarabine batch numbers:

Ara cell®: 4N296E5, 4N295E5, 4D276F4, 4C269D4, 3K258M3, 3H24713, 3H246I3, 14HA7324, 3D233E3, 2M226D3, 2K221M2, 2D205G2, 1N196E2, 1I184J1, 1F177H1, 0N165C1

Endpoints/Outcomes

Primary Endpoint: Event-free survival, defined as time until disease recurrence, treatment failure or death (due to any cause), whichever occurs first.

Secondary endpoints: overall survival, relapse-free survival, mortality, rate of engraftment, kinetics of chimerism, any events of cardiac toxicity from the first administration of IMP until day 30 after SCT

Safety Endpoints: All reported Adverse or Serious Adverse Events. Events were reported from the first administration of IMP until 30 days after SCT.

Statistical methods:

Efficacy: The type I error is set to 5% (two-sided). No interim analyses were planned for this trial.

Primary Endpoint: The endpoint time-to-first-event is analysed with a Log-rank test stratified for centre and remission state. In addition, the corresponding two-sided 95%-confidence-interval for the hazard ratio (ClAraC vs. FLAMSA) is calculated. ClAraC is superior to FLAMSA if the upper boundary of this confidence interval is below 1. In addition, for sensitivity analyses, cox regression models are calculated.

Key Secondary Endpoints:

1. (a) Overall survival and (b) Relapse free survival is analysed with Cox regression models.
2. Events of cardiac toxicity from the first administration of IMP until day 30 after SCT is analysed with a two-sided 95% confidence intervals from a logistic regression model for the odds ratio (ClAraC vs. FLAMSA).
3. Rate of engraftment is analysed with a two-sided 95% confidence intervals from a logistic regression model for the odds ratio (ClAraC vs. FLAMSA) is calculated.
4. Kinetics of chimerism after allogeneic stem cell transplantation was planned to be analysed with a linear regression model. However chimerism is better described as a dichotomous variable (100% vs <100%) and therefore is analysed with a logistic regression model.

All secondary analyses are adjusted for remission state and, if the model converged, for centre.

Safety: All Adverse and Severe Adverse Events are grouped per treatment arm. Absolute and relative frequencies are reported at the event and at the patient level. In addition for the comparison at the patient level p-values of χ^2-test are calculated.

All analyses have been performed with SAS 9.3.

Primary analysis population characteristics

A total of 62 patients were included into the trial. 2 patients did not meet the inclusion/exclusion criteria so that only 60 patients were randomized to the ClAraC or FLAMSA treatment regimen. These 60 patients serve as the ITT population in this trial. One patient in the ClAraC treatment arm was lost to follow up.

All patients, except the patient that was lost to follow up, were observed until death or a minimum observation time of approximately 18 months.

Population characteristics are based on the ITT population.

Variable	ClAraC (n=30)	FLAMSA (n=30)	Total (n=60)
Sex (female)	16 (53.3%)	17 (56.7%)	33 (55.0%)
Race			
Caucasian	30(100%)	28 (93.3%)	58 (96.7%)
Asian	0 (0%)	1 (3.3%)	1 (1.7%)
Other	0 (0%)	1 (3.3%)	1 (1.7%)
Remission strate			
AML with complete remission*	9 (30.0%)	8 (26.7%)	17 (28.3%)
Center			
Hannover	21 (70.0%)	21 (70.0%)	42 (70.0%)
Leipzig	6 (20.0%)	7 (23.3%)	13 (21.7%)
Jena	3 (10.0%)	2 (6.7%)	5 (8.3%)
Height [cm]	172.2±9.5	173.1±9.4	172.6±9.4
Weight [kg]	76.2±19.6	79.3±17.6	77.8±18.5
Body Surface Area	1.89±0.28	1.95±0.24	1.92±0.26
Age [years]	55.1±9.9	53.0±10.4	54.1±10.1
HLA-match (HLA-identical)	24 (80.0%)	29 (96.7%)	53 (88.3%)
Donor (related)	8 (26.7%)	7 (23.3%)	15 (25.0%)
ECOG*			
Grade 0	15 (53.6%)	17 (58.6%)	32 (56.1%)
Grade 1	10 (35.7%)	8 (27.6%)	18 (31.6%)
Grade 2	3 (10.7%)	4 (13.8%)	7 (12.3%)

* During the data review process, a total of 3 patients were identified that were allocated by the treating physion to the wrong remission state group. These patient were analysed as randomized.

** For ECOG some baseline values were missing (n=2 inClAraC, n=1 in FLAMSA). Relative frequencies are based on patients with available ECOG.

Treatment groups were well-balanced for the aforementioned baseline variables.

Efficacy results:

Analysis of the efficacy results is based on the ITT population (all randomized patients). We identified only 4 patients for exclusion in a per protocol analysis (1 patient whose therapy was stopped due to a sepsis and the above mentioned 3 patients that were allocated by the treating physician to the wrong stratum with respect to the remission state). In consequence no additional analysis in the per protocol population is provided.

Primary Endpoint

Event-free survival is defined as time until disease recurrence, treatment failure or death (due to any cause), whichever occurs first. One patient was lost to follow up and will be counted as treatment failure in the analyses.

All recorded events which are relevant for the definition of event-free survival are shown in the following table. The total number of events is not necessarily the sum of the individual events because multiple events can occur (e.g. recurrence and death).

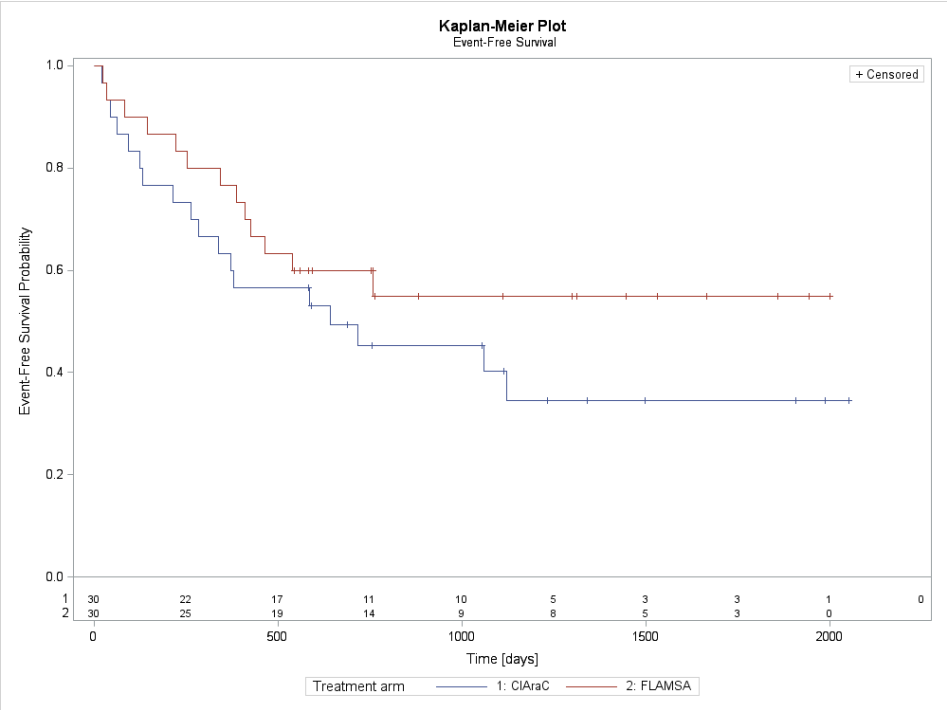
Treatment arm	No. of Events	No. of Censorings	No. of recurrences	No. of treatment failures	No. of lost patients	No. of Deaths
ClAraC (n=30)	18	12	7	1	1	16
FLAMSA (n=30)	13	17	6	1	0	12

Median and mean event-free survival times are presented in the following table. Median survival was not reached in the FLAMSA arm.

	ClAraC	FLAMSA
Median [days]	643	not reached
Mean ± SE time to event [days]	656.6 ± 84.6	565.6 ± 49.2

Calculation of the Hazard Ratio is based on observed and expected events (Altman, 1991, Practical Statistics for Medical Research, pp. 381-382): HR=1.55, 95% confidence interval (0.76, 3.13). ClAraC is numerically inferior to FLAMSA.

The Logrank-test to compare the two treatment arms yields to a two-sided p-value of 0.1774 (stratified for center and remission state). The following Kaplan-Meier plot shows the event-free survival curves for both treatment arms.



In addition, several Cox regression models are presented to compare ClAraC and FLAMSA. Computation of the confidence intervals of the Hazard Ratio was based on the profile likelihood. The Hazard ratio remained constant across the investigated models. To explore the treatment effect, calculations were repeated in subgroups formed by remission state (> 5%, or ≤5% blasts).

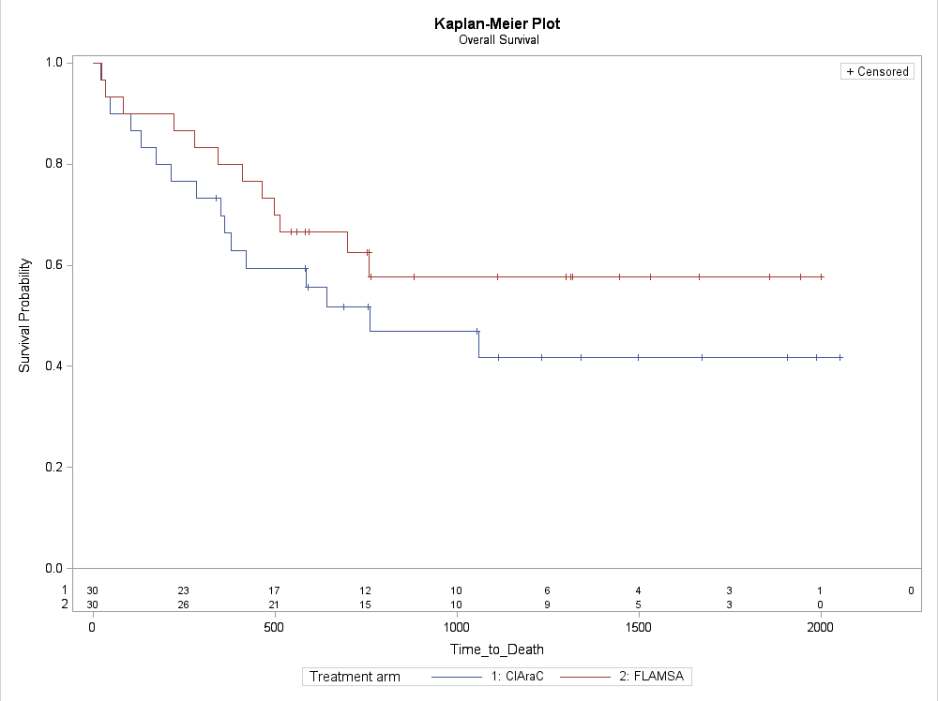
Model: event free survival	ClAraC No. Events / No. Patients	FLAMSA No. Events / No. Patients	HR for treatment, (95% CI)	p-value
all patients, adjusted for center and remission state	18/30	13/30	1.551, (0.759, 3.254)	0.2326
unadjusted, subgroup of patients with ≤5% blasts	6/9	3/8	1.788, (0.471, 8.488)	0.4120
unadjusted, subgroup of patients with>5% blasts	12/21	10/22	1.470, (0.633, 3.488)	0.3691

Sensitivity analyses were consistent with the primary analysis of the trial and demonstrate that ClaraC was numerically inferior to FLAMSA with an approximately 3 month mean difference in event free survival.

Overall Survival

Overall survival is defined as time from randomisation until date of death due to any cause. Living patients were censored at the end of the trial. 16/30 (53.3%) patients died until the end of the study in the ClAraC treatment arm, whereas only 12/30 (40.0%) died in the FLAMSA treatment arm.

The stratified Logrank-test yields a P-value of 0.1344. The following Kaplan-Meier plot shows overall survival curves for ClAraC and FLAMSA.

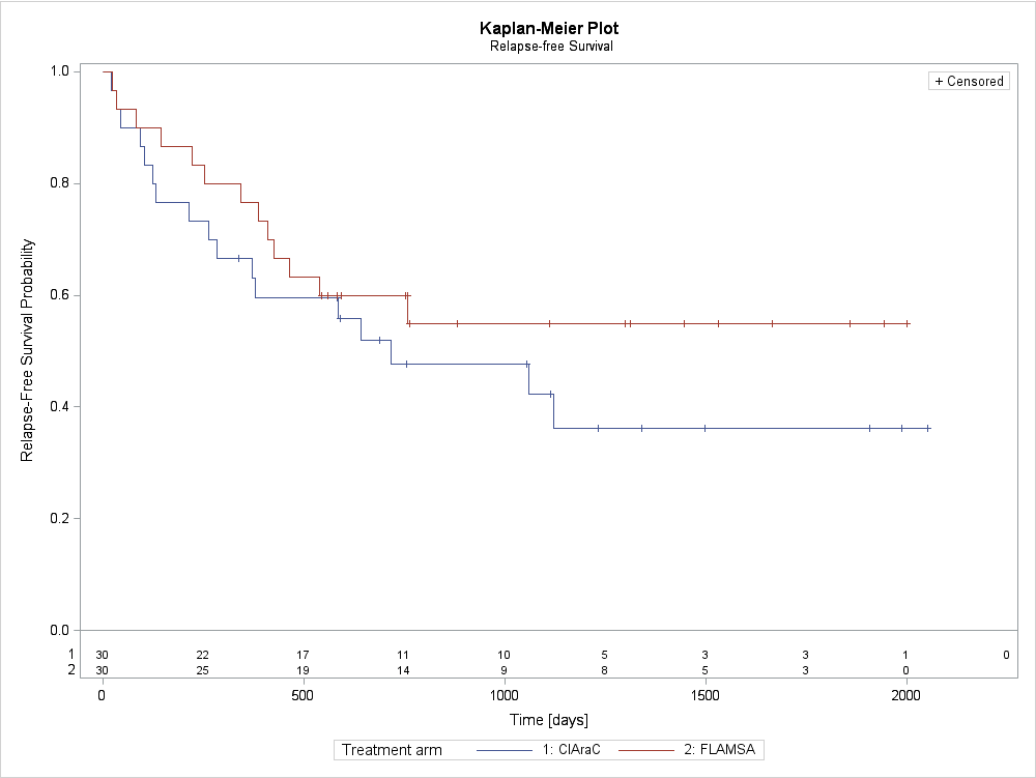


Results of the adjusted Cox regression model for time-to-death are presented for all patients in the following table. In addition, results for the subgroups regarding remission state are presented:

Model: Overall survival	**ClAraC No. Events / No. Patients**	**FLAMSA No. Events / No. Patients**	**HR for treatment, (95% CI)**	**p-value**
adjusted for center and remission state, all patients	16/30	12/30	1.579, (0.745, 3.434)	0.2357
unadjusted, subgroup patients with ≤5% blasts	6/9	2/8	2.758, (0.634, 18.834)	0.2145
unadjusted, subgroup patients with>5% blasts	10/21	10/22	1.260, (0.516, 3.076)	0.6065

Secondary Endpoint: Relapse-free Survival

Relapse-free survival is defined as time from randomization until the date of first objective documentation of disease recurrence or death due to any cause, whichever occurs first. Patients were censored at the end of the trial if no event had been observed. The p-value of the stratified Logrank-test is 0.2518.



A stratified Cox regression model was used to compare the two treatment arms. The model shows a Hazard Ratio > 1 for the experimental treatment.

Model: Relapse free survival	**ClAraC No. Events / No. Patients**	**FLAMSA No. Events / No. Patients**	**HR for treatment, (95% CI)**	**p-value**
adjusted for center and remission state, all patients	17/30	13/30	1.459, (0.706, 3.084)	0.3101

Secondary Endpoint: Cardiac toxicity

Cardiac toxicity was observed from the first administration of IMP until day 30 after SCT. 26 patients were affected in the ClAraC treatment arm, whereas 27 patients were affected in the FLAMSA treatment arm (see table “Number of patients with at least one cardiac toxic event”). A logistic regression analysis was performed to compare the two treatment arms. The stratified analysis included only remission state and not center due to convergence problems for maximum likelihood estimates of variable center.

Model: Cardiac toxicity	**ClAraC No. Events / No. Patients**	**FLAMSA No. Events / No. Patients**	**OR for treatment, (95% CI)**	**p-value**
adjusted for remission state, all patients	26/30	27/30	0.750, (0.146, 3.846)	0.7304

Secondary Endpoint (Rate of Engraftment)

Engraftment was defined in the study protocol by leukocytes > 1.000/µl or neutrophils >500/µl during the course of the study. However, in order to comply with more recent EBMT guidelines, the definition of only neutrophils > 500/µl seems to be more suitable. Both definitions lead to the same results: 28 patients reached an engraftment in each study arm. The only difference was the time point when the success criterion was reached. Analyses are based on the ITT set. Note that for the logistic regression models the probability for an engraftment is modelled. Therefore an Odds Ratio > 1 is favourable.

Results of the logistic regression analysis are shown in the following table. The model is only stratified for remission state due to convergence problems.

Model: rate of engraftment	**ClAraC No. Events /No. Patients**	**FLAMSA No. Events /No. Patients**	**OR for treatment, 95% CI**	**p-value**
adjusted for remission state, all patients	28/30	28/30	1.04, (0.134, 8.056)	0.9704

There was no differece between the two treatment strategies.

Secondary Endpoint (Kinetics of chimerism after SCT)

Analysis of chimerism refers to the measurement of donor cells after SCT. If the transplantation is successful, it is anticipated that the percentage of donor cells will ideally be at 100%. The more the measurement deviates from 100% (i.e. decreases), the more likely is a relapse of the disease.

Results are presented for the 18 months time-point (the minimum observation time of the trial) because it is of interest whether the patients develop an early relapse and are able to keep the transplant over time. A substantial amount of information was missing values (26 out of 60). In order to comply with the ITT principle, a LOCF-based imputation strategy was applied (if a value was available the last observation was carried forward, if no observation was available 0 was imputed). The analysis was planned as a regression analysis. However, it was discovered that most measurements (if available) are 100% or close to 100%, so that a linear regression is not suitable. Therefore, we performed logistic regression analyses with dependent variable 100% donor cells (yes/no).
An Odds Ratio >1 indicates numerically favourable outcome for the experimental treatment group. Results do not suggest differences between treatments and were inconsistently depending on the method for replacement of missing values.

Model: chimerism	**ClAraC No. Events /No. Patients**	**FLAMSA No. Events /No. Patients**	**OR for treatment, 95% CI**	**p-value**
Logistic regression, adjusted for remission state, all patients	11/30	10/30	1.173 (0.404, 3.404)	0.7698
Logistic regression, unadjusted, subgroup patients with ≤5% blasts	3/9	2/8	1.500, (0.181, 12.459)	0.7074
Logistic regression, unadjusted, subgroup patients with>5%	8/21	8/22	1.077, (0.313, 3.710)	0.9065

blasts				
Logistic regression, adjusted for remission state, only patients with non-missing values	1/14	2/20	0.611, (0.046, 8.048)	0.7078

Laboratory toxicity

Acute toxicity (lab measurement at time points IMP, RIC and Allo-SCT) and concomitant toxicity (lab measurement at time points IMP, RIC, Allo-SCT, day 15 and day 30 after Allo-SCT) were compared between ClAraC and FLAMSA using descriptive statistics and two-sided t-tests with respective mean difference. Neutrophil count was calculated as WBC count times Neutrophil (percentage). The minimum per patient was calculated over the given time points for hematologic lab values. In contrast to that, the maximum per patient was calculated across the time points for parameters from the other three areas (liver, kidney, hyperkalemia).

		ClAraC			FLAMSA			t-test (ClAraC-FLAMSA)	
	Variable	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**Mean Diff**	**p-value**
Hematology (minimum value per patient)	WBC (acute)	30	0.06	0.19	30	0.03	0.05	0.03	0.3504
	WBC (concomitant)	30	0.06	0.19	30	0.02	0.05	0.04	0.3036
	Hemoglobin (acute)	30	7.86	0.68	30	8.27	0.84	-0.41	0.0434
	Hemoglobin (concomitant)	30	7.68	0.83	30	7.99	0.60	-0.31	0.0994
	Thrombocytes (acute)	30	13.10	7.73	30	12.30	6.77	0.80	0.6714
	Thrombocytes (concomitant)	30	13.00	7.79	30	12.03	6.96	0.97	0.6141
	Neutrophil count (acute)	26	207.08	268.96	27	138.19	202.72	68.89	0.2962
	Neutrophil count (concomitant)	30	74.41	93.02	30	79.75	113.77	-5.34	0.8430
Liver (maximum value per patient)	ALT (acute)	30	113.03	140.47	30	56.77	58.48	56.26	0.0475
	ALT (concomitant)	30	123.36	141.84	30	59.77	57.66	63.59	0.0266
	AST (acute)	30	71.22	120.68	30	33.23	22.90	37.99	0.0956
	AST (concomitant)	30	79.17	119.05	30	37.22	22.36	41.95	0.0629
	Bilirubin (acute)	30	18.37	14.11	30	14.86	9.90	3.51	0.2697
	Bilirubin (concomitant)	30	19.39	13.67	30	16.77	12.96	2.62	0.4486
Kidney (maximum value per patient)	Creatinine (acute)	30	80.57	22.74	30	77.50	15.22	3.07	0.5417
	Creatinine (concomitant)	30	109.97	35.87	30	101.77	35.74	8.20	0.3788
Hyper-kalemia (maximum value per patient)	Potassium (acute)	30	4.45	0.34	30	4.51	0.32	-0.07	0.4505
	Potassium (concomitant)	30	4.60	0.41	30	4.58	0.29	0.03	0.7800

Safety results:

Adverse events were classified into three categories and were reported separately: Cardiac Toxicity Adverse Events, Expected Leukaemia Adverse Events, and General Adverse Events. In addition,

Serious Adverse Events are presented without any categorization into the aforementioned three categories. All tabulated Adverse Events are presented by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA 20.0. Severity of adverse events was be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 Sequential events or events with overlapping time periods are summarized, if patient and Preferred Term are equal. In case events were summarized, the earliest start date, latest end date and worst event characteristic (CTCAE grade) are used.

The safety analysis was performed in the ITT population. A total of 2352 adverse events (1585 general adverse events, 153 cardiac toxicity adverse events and 614 expected leukemia adverse events) were observed in 60 patients. Most adverse events (57.5% overall) were suspected to have a causal relationship to the respective study medication. In total 38 of the adverse events were serious adverse events. In the ClAraC group 4 patients had a fatal outcome and 3 in the FLAMSA group.

For all three categories and for the serious adverse events, the tables showing the total number of events and number of patients with at least one event are provided. The following analysis reports on observed AEs and SAEs up to 30 days after SCT. In this time frame, 3 patients in the ClAraC treatment arm and 2 patients in the FLAMSA treatment arm died. 1 patient in the ClAraC and 1 patient in the FLAMSA treatment arm had ongoing SAEs which were fatal beyond 30 days after SCT.

General Adverse Events

1. Number of events:

General AE Events	Treatment arm - CODELIST		
	ClAraC N=30	FLAMSA N=30	Total N=60
Total Number of AEs	874	711	1585
... AE with Outcome: not recovered (persistently not changing)	22 (2.5%)	8 (1.1%)	30 (1.9%)
... AE with suspected causal relationship to study medication	434 (49.7%)	366 (51.4%)	800 (50.5%)

2. Number of patients with at least one event:

General AE Events	Treatment arm			
	ClAraC N=30	FLAMSA N=30	Total N=60	p-Wert[1]
Number of patients with at least one ...				
... AE	30 (100.0%)	30 (100.0%)	60 (100.0%)	
... AE with Outcome: fatal	3 (10.0%)	2 (6.7%)	5 (8.3%)	0.6404
... AE with Outcome: not recovered (persistently not changing)	5 (16.7%)	1 (3.3%)	6 (20.0%)	0.0852
... AE with suspected causal relationship to study medication	29 (96.7%)	29 (96.7%)	58 (96.7%)	1.0000

[1] **p-value of Chi-squared tests**

3. Outcome:

General AE Events

	Treatment		
	ClAraC N=30	**FLAMSA N=30**	**Total N=60**
Total number of AE	874	711	1585
completely recovered/back to baseline conditions	823 (94.2%)	664 (93.4%)	1487 (93.8%)
recovered with sequel	20 (2.3%)	36 (5.1%)	56 (3.5%)
not recovered (persistently not changing)	22 (2.5%)	8 (1.1%)	30 (1.9%)
unknown	1 (0.1%)	0 (0.0%)	1 (0.0%)
fatal	8 (0.9%)	3 (0.4%)	11 (0.1%)

Table includes all general adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

4. Impact of the event on study treatment and further actions:

General AE Events

	Treatment		
	ClAraC N=30	**FLAMSA N=30**	**Total N=60**
Total number of AE	874	711	1585
Action taken regarding study medication			
- None	862 (98.6%)	708 (99.6%)	1570 (99.1%)
- Dose reduced	2 (0.2%)	1 (0.1%)	3 (0.2%)
- Study drug interrupted and restarted	4 (0.5%)	0 (0.0%)	4 (0.3%)
- Study drug discontinued	6 (0.7%)	2 (0.3%)	8 (0.5%)
Other actions taken: Concomitant medication			
- No	466 (53.3%)	344 (48.4%)	810 (51.1%)
- Yes	408 (46.7%)	367 (51.6%)	775 (48.9%)
Other actions taken: Therapeutic or diagnostic measures (except medication)			
- No	662 (75.7%)	556 (78.2%)	1218 (76.9%)
- Yes	212 (24.3%)	155 (21.8%)	367 (23.1%)

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

5. Number of CTC grades:

Number of events (General AE)

	Treatment		
CTC Grade	**ClAraC N=30**	**FLAMSA N=30**	**Total N=60**
Total number of AE	874	711	1585
Not determined	1 (0.1%)	3 (0.4%)	4 (0.3%)
1	530 (60.6%)	452 (63.6%)	982 (62.0%)
2	249 (28.5%)	189 (26.5%)	438 (27.6%)
3	78 (8.9%)	50 (7.0%)	128 (8.1%)
4	8 (0.9%)	14 (2.0%)	22 (1.4%)
5	8 (0.9%)	3 (0.4%)	11 (0.7%)

Table includes all general adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

6. Maximum observed CTC grade per patient:

Number of events (General AE)

	Treatment		
CTC Grade	**ClAraC N=30**	**FLAMSA N=30**	**Total N=60**
Number of patient with at least one AE	30	30	60
1	0 (0.0%)	1 (3.3%)	1 (1.7%)
2	5 (16.6%)	10 (33.3%)	15 (25.0%)
3	20 (66.7%)	13 (43.3%)	33 (55.0%)
4	2 (6.7%)	4 (13.3%)	6 (0.1%)
5	3 (0.1%)	2 (6.7%)	5 (8.3%)

Table includes only one adverse event per patient (maximum ctc-grade). Percentages are calculated using the total number of events per treatment group as the denominator.

Cardiac Toxicity

1. Number of events:

Cardiac Toxic Events	Treatment arm

	ClAraC N=30	FLAMSA N=30	Total N=60
Total Number of AEs	82	71	153
... AE with Outcome: not recovered (persistently not changing)	3 (3.7%)	0 (0.0%)	3 (2.0%)
... AE with suspected causal relationship to study medication	56 (68.3%)	43 (60.6%)	99 (64.7%)

2. Number of patients with at least one event :

Cardiac Toxic Events	Treatment arm			
	ClAraC N=30	FLAMSA N=30	Total N=60	p-Wert[1]
Number of patients with at least one ...				
... AE	26 (86.7%)	27 (90.0%)	53 (88.3%)	0.6876
... AE with Outcome: fatal	2 (6.7%)	0 (0.0%)	2 (3.3%)	0.1503
... AE with Outcome: not recovered (persistently not changing)	2 (6.7%)	0 (0.0%)	2 (3.3%)	0.1503
... AE with suspected causal relationship to study medication	21 (70.0%)	19 (63.3%)	40 (66.7%)	0.5839

[1] **p-value of Chi-squared tests**

3. Outcome:

Cardiac Toxic Events	Treatment arm		
	ClAraC N=30	FLAMSA N=30	Total N=60
Total number of AE	82	71	153
completely recovered/back to baseline conditions	72 (87.8%)	64 (90.1%)	136 (88.8%)
recovered with sequel	5 (6.1%)	7 (9.9%)	12 (7.8%)
not recovered (persistently not changing)	3 (3.6%)	0 (0.0%)	3 (1.9%)
fatal	2 (2.4%)	0 (0.0%)	2 (1.3%)

Table includes all general adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

4. Impact of the event on study treatment and further actions:

Cardiac Toxic Events

	Treatment arm		
	ClAraC N=30	**FLAMSA N=30**	**Total N=60**
Total number of AE	82	71	153
Action taken regarding study medication			
- None	81 (98.8%)	71 (100.0%)	152 (99.3%)
- Study drug interrupted and restarted	1 (1.2%)	0 (0.0%)	1 (0.6%)
Other actions taken: Concomitant medication			
- No	41 (50.0%)	44 (62.0%)	85 (55.5%)
- Yes	41 (50.0%)	27 (38.0%)	68 (44.4%)
Other actions taken: Therapeutic or diagnostic measures (except medication)			
- No	56 (68.3%)	61 (85.9%)	117 (76.4%)
- Yes	26 (31.7%)	10 (14.1%)	36 (23.6%)

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

5. Number of CTC grades

:**Number of events (Cardiac Toxic)**

	Treatment		
CTC Grade	**ClAraC N=30**	**FLAMSA N=30**	**Total N=60**
Total number of AE	82	71	153
1	32 (39.0%)	39 (54.9%)	71 (46.4%)
2	33 (40.2%)	28 (39.4%)	61 (39.9%)
3	13 (15.8%)	4 (5.6%)	17 (11.1%)
4	2 (2.4%)	0 (0.0%)	2 (1.3%)
5	2 (2.4%)	0 (0.0%)	2 (1.3%)

Table includes all general adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

6. Maximum observed CTC grade per patient:

Number of patients (Cardiac Toxic)

Treatment

CTC Grade	ClAraC N=30	FLAMSA N=30	Total N=60
Number of patient with at least one AE	26	27	53
1	3 (11.5%)	7 (25.9%)	10 (18.9%)
2	13 (50.0%)	16 (59.3%)	29 (54.7%)
3	8 (30.8%)	4 (14.8%)	12 (22.6%)
5	2 (7.7%)	0 (0.0%)	2 (3.7%)

Table includes only one adverse event per patient (maximum ctc-grade). Percentages are calculated using the total number of events per treatment group as the denominator.

Expected Leukemia

1. Number of events:

Expected Leukemia Events	Treatment arm - CODELIST		
	ClAraC N=30	FLAMSA N=30	Total N=60
Total Number of AEs	310	304	614
... AE with Outcome: not recovered (persistently not changing)	2 (0.6%)	1 (0.3%)	3 (0.5%)
... AE with suspected causal relationship to study medication	237 (76.5%)	217 (71.4%)	454 (73.9%)

2. Number of patients with at least one event:

Expected Leukemia Events	Treatment arm			
	ClAraC N=30	FLAMSA N=30	Total N=60	p-Wert[1]
Number of patients with at least one ...				
... AE	30 (100.0%)	30 (100.0%)	60 (100.0%)	
... AE with Outcome: fatal	1 (3.3%)	1 (3.3%)	2 (3.3%)	1.0000
... AE with Outcome: not recovered (persistently not changing)	1 (3.3%)	1 (3.3%)	2 (3.3%)	1.0000
... AE with suspected causal relationship to study medication	29 (96.7%)	29 (96.7%)	58 (96.7%)	1.0000

[1] **p-value of Chi-squared tests**

3. Outcome:

Expected Leukemia Events

	Treatment arm		
	ClAraC N=30	**FLAMSA N=30**	**Total N=60**
Total number of AE	310	304	614
completely recovered/back to baseline conditions	272 (87.7%)	247 (84.2%)	528 (86.0%)
recovered with sequel	35 (11.3%)	46 (15.1%)	81 (13.2%)
not recovered (persistently not changing)	2 (0.6%)	1 (0.3%)	3 (0.4%)

Table includes all general adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

4. Impact of the event on study treatment and further actions:

Expected Leukemia Events

	Treatment arm		
	ClAraC N=30	**FLAMSA N=30**	**Total N=60**
Total number of AE	310	304	614
Action taken regarding study medication			
- None	309 (99.7%)	304 (100.0%)	613 (99.8%)
- Study drug interrupted and restarted	1 (0.3%)	0 (0.0%)	1 (0.2%)
Other actions taken: Concomitant medication			
- No	139 (44.8%)	141 (46.4%)	280 (45.6%)
- Yes	171 (55.2%)	163 (53.6%)	334 (54.4%)
Other actions taken: Therapeutic or diagnostic measures (except medication)			
- No	237 (76.5%)	234 (77.0%)	471 (76.7%)
- Yes	73 (23.5%)	70 (23.0%)	143 (23.6%)

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

5. Number of CTC grades:

Number of events (Expected Leukemia)

CTC Grade	Treatment ClAraC N=30	FLAMSA N=30	Total N=60
Total number of AE	310	304	614
1	164 (52.9%)	175 (57.6%)	339 (55.2%)
2	96 (31.0%)	76 (25.0%)	172 (28.0%)
3	27 (8.7%)	18 (5.9%)	45 (7.3%)
4	22 (7.1%)	34 (11.2%)	56 (9.1%)
5	1 (0.3%)	1 (0.3%)	2 (0.3%)

Table includes all general adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

6. Maximum CTC grade per patient:

Number of patients (Expected Leukemia)

CTC Grade	Treatment ClAraC N=30	FLAMSA N=30	Total N=60
Number of patient with at least one AE	30	30	60
1	1 (3.3%)	3 (3.3%)	4 (6.7%)
2	16 (53.3%)	17 (56.7%)	33 (55.0%)
3	4 (13.3%)	1 (3.3%)	5 (8.3%)
4	8 (26.7%)	8 (26.7%)	16 (26.7%)
5	1 (3.3%)	1 (3.3%)	2 (3.3%)

Table includes only one adverse event per patient (maximum ctc-grade). Percentages are calculated using the total number of events per treatment group as the denominator.

Serious Adverse Events

1. Number of serious adverse events:

SAE Events	Treatment arm ClAraC N=30	FLAMSA N=30	Total N=60
Total Number of SAEs	20	18	38
... SAE with Outcome: fatal	11 (55.0%)	4 (22.2%)	15 (39.5%)
... SAE with Outcome: not recovered (persistently not changing)	1 (5.0%)	0 (0.0%)	1 (2.6%)
... SAE with suspected causal relationship to study medication	1 (5.0%)	7 (38.9%)	8 (21.1%)

2. Number of patients with at least one Serious Adverse Event:

SAE Events	Treatment arm			
	ClAraC N=30	FLAMSA N=30	Total N=60	p-Wert[1]
Number of patients with at least one ...				
... SAE with Outcome: fatal	4 (13.3%)	3 (10.0%)	7 (11.7%)	0.6876
... SAE with Outcome: not recovered (persistently not changing)	1 (3.3%)	0 (0.0%)	1 (1.7%)	0.3136
... SAE with suspected causal relationship to study medication	1 (3.3%)	4 (13.3%)	5 (8.3%)	0.1611

[1] **p-value of Chi-squared tests**

Overall Conclusion:

This study did compare two different conditioning regimens for allogeneic stem cell recipients with high risk AML/MDS. 62 patients have been included and 60 were randomized. The treatment arms were well-balanced at study baseline for relevant co-variates. Superiority of the ClAraC treatment regimen over the FLAMSA regimen could not be demonstrated. Consistently Hazard Ratios for event free survival, overall survival and relapse-free survival were in favour of the control group with FLAMSA treatment. No differences were found regarding cardiac toxicity, rate of engraftment, or chimerism. Regarding general safety parameters, no relevant differences between the two treatment strategies were found.

Date of report: 14.05.2018

3 Appendix

General AE

Number of events (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Total number of AE	874	711	1585
Blood and lymphatic system disorders	4 (0.5%)	3 (0.4%)	7 (0.4%)
Coagulopathy	1 (0.1%)	-	1 (0.1%)
Febrile neutropenia	-	1 (0.1%)	1 (0.1%)
Hilar lymphadenopathy	1 (0.1%)	-	1 (0.1%)
Lymphadenopathy	-	1 (0.1%)	1 (0.1%)
Splenomegaly	2 (0.2%)	-	2 (0.1%)
Thrombotic thrombocytopenic purpura	-	1 (0.1%)	1 (0.1%)
Cardiac disorders	5 (0.6%)	8 (1.1%)	13 (0.8%)
Bradycardia	2 (0.2%)	-	2 (0.1%)
Cardiomegaly	-	1 (0.1%)	1 (0.1%)
Cardiovascular insufficiency	-	1 (0.1%)	1 (0.1%)
Cyanosis	-	1 (0.1%)	1 (0.1%)
Pericardial effusion	-	1 (0.1%)	1 (0.1%)
Sinus bradycardia	1 (0.1%)	-	1 (0.1%)
Sinus tachycardia	-	1 (0.1%)	1 (0.1%)
Tachycardia	2 (0.2%)	2 (0.3%)	4 (0.3%)
Ventricular tachycardia	-	1 (0.1%)	1 (0.1%)
Ear and labyrinth disorders	10 (1.1%)	7 (1.0%)	17 (1.1%)
Deafness neurosensory	1 (0.1%)	-	1 (0.1%)
Hypoacusis	-	2 (0.3%)	2 (0.1%)
Middle ear effusion	1 (0.1%)	-	1 (0.1%)
Vertigo	8 (0.9%)	5 (0.7%)	13 (0.8%)
Endocrine disorders	1 (0.1%)	2 (0.3%)	3 (0.2%)
Adrenal disorder	-	1 (0.1%)	1 (0.1%)
Hyperthyroidism	1 (0.1%)	1 (0.1%)	2 (0.1%)
Eye disorders	13 (1.5%)	12 (1.7%)	25 (1.6%)
Conjunctival oedema	1 (0.1%)	-	1 (0.1%)
Dry eye	3 (0.3%)	3 (0.4%)	6 (0.4%)
Eye haemorrhage	-	1 (0.1%)	1 (0.1%)
Eye irritation	1 (0.1%)	1 (0.1%)	2 (0.1%)
Eyelid oedema	2 (0.2%)	3 (0.4%)	5 (0.3%)
Lacrimation increased	2 (0.2%)	1 (0.1%)	3 (0.2%)
Ocular discomfort	1 (0.1%)	-	1 (0.1%)
Ocular hyperaemia	2 (0.2%)	-	2 (0.1%)
Photopsia	-	1 (0.1%)	1 (0.1%)
Vision blurred	1 (0.1%)	-	1 (0.1%)
Visual impairment	-	1 (0.1%)	1 (0.1%)

Number of events (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Vitreous haemorrhage	-	1 (0.1%)	1 (0.1%)
Gastrointestinal disorders	135 (15.4%)	143 (20.1%)	278 (17.5%)
Abdominal discomfort	4 (0.5%)	6 (0.8%)	10 (0.6%)
Abdominal distension	1 (0.1%)	2 (0.3%)	3 (0.2%)
Abdominal pain	18 (2.1%)	15 (2.1%)	33 (2.1%)
Abdominal pain upper	10 (1.1%)	21 (3.0%)	31 (2.0%)
Anorectal disorder	1 (0.1%)	-	1 (0.1%)
Aphthous ulcer	1 (0.1%)	-	1 (0.1%)
Ascites	1 (0.1%)	-	1 (0.1%)
Coating in mouth	-	1 (0.1%)	1 (0.1%)
Constipation	25 (2.9%)	21 (3.0%)	46 (2.9%)
Diarrhoea	39 (4.5%)	33 (4.6%)	72 (4.5%)
Dry mouth	2 (0.2%)	1 (0.1%)	3 (0.2%)
Dyspepsia	1 (0.1%)	8 (1.1%)	9 (0.6%)
Dysphagia	2 (0.2%)	2 (0.3%)	4 (0.3%)
Enteritis	-	1 (0.1%)	1 (0.1%)
Epigastric discomfort	-	1 (0.1%)	1 (0.1%)
Eructation	1 (0.1%)	-	1 (0.1%)
Flatulence	3 (0.3%)	2 (0.3%)	5 (0.3%)
Gastric disorder	-	2 (0.3%)	2 (0.1%)
Gastritis	1 (0.1%)	-	1 (0.1%)
Gastrooesophageal reflux disease	3 (0.3%)	2 (0.3%)	5 (0.3%)
Haemorrhoids	4 (0.5%)	2 (0.3%)	6 (0.4%)
Impaired gastric emptying	1 (0.1%)	-	1 (0.1%)
Lip blister	-	1 (0.1%)	1 (0.1%)
Lip pruritus	-	1 (0.1%)	1 (0.1%)
Lip swelling	-	1 (0.1%)	1 (0.1%)
Melaena	1 (0.1%)	-	1 (0.1%)
Mouth haemorrhage	-	1 (0.1%)	1 (0.1%)
Mouth swelling	2 (0.2%)	-	2 (0.1%)
Mouth ulceration	1 (0.1%)	-	1 (0.1%)
Nausea	-	2 (0.3%)	2 (0.1%)
Odynophagia	1 (0.1%)	1 (0.1%)	2 (0.1%)
Oesophageal pain	1 (0.1%)	1 (0.1%)	2 (0.1%)
Oesophagitis	1 (0.1%)	1 (0.1%)	2 (0.1%)
Oral discomfort	3 (0.3%)	1 (0.1%)	4 (0.3%)
Oral mucosal blistering	1 (0.1%)	1 (0.1%)	2 (0.1%)
Oral mucosal erythema	2 (0.2%)	-	2 (0.1%)
Oral pain	-	1 (0.1%)	1 (0.1%)
Pancreatitis	1 (0.1%)	-	1 (0.1%)
Proctalgia	1 (0.1%)	-	1 (0.1%)
Small intestinal obstruction	-	1 (0.1%)	1 (0.1%)
Stomatitis	-	2 (0.3%)	2 (0.1%)
Tongue coated	2 (0.2%)	1 (0.1%)	3 (0.2%)
Tongue ulceration	-	2 (0.3%)	2 (0.1%)
Toothache	-	1 (0.1%)	1 (0.1%)
Vomiting	-	4 (0.6%)	4 (0.3%)

Number of events (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
General disorders and administration site conditio	159 (18.2%)	142 (20.0%)	301 (19.0%)
Administration site papule	1 (0.1%)	-	1 (0.1%)
Asthenia	2 (0.2%)	1 (0.1%)	3 (0.2%)
Axillary pain	1 (0.1%)	1 (0.1%)	2 (0.1%)
Catheter site erythema	3 (0.3%)	6 (0.8%)	9 (0.6%)
Catheter site haematoma	1 (0.1%)	2 (0.3%)	3 (0.2%)
Catheter site haemorrhage	3 (0.3%)	3 (0.4%)	6 (0.4%)
Catheter site inflammation	-	1 (0.1%)	1 (0.1%)
Catheter site pain	9 (1.0%)	8 (1.1%)	17 (1.1%)
Catheter site related reaction	-	2 (0.3%)	2 (0.1%)
Catheter site swelling	1 (0.1%)	4 (0.6%)	5 (0.3%)
Chest discomfort	2 (0.2%)	1 (0.1%)	3 (0.2%)
Chest pain	7 (0.8%)	10 (1.4%)	17 (1.1%)
Chills	16 (1.8%)	22 (3.1%)	38 (2.4%)
Disease progression	1 (0.1%)	-	1 (0.1%)
Early satiety	-	2 (0.3%)	2 (0.1%)
Face oedema	2 (0.2%)	1 (0.1%)	3 (0.2%)
Facial pain	-	2 (0.3%)	2 (0.1%)
Fatigue	32 (3.7%)	25 (3.5%)	57 (3.6%)
Feeling hot	2 (0.2%)	1 (0.1%)	3 (0.2%)
Gait disturbance	2 (0.2%)	-	2 (0.1%)
Injection site extravasation	1 (0.1%)	-	1 (0.1%)
Injection site reaction	1 (0.1%)	-	1 (0.1%)
Malaise	3 (0.3%)	1 (0.1%)	4 (0.3%)
Mucosal dryness	1 (0.1%)	1 (0.1%)	2 (0.1%)
Mucosal haemorrhage	-	1 (0.1%)	1 (0.1%)
Mucosal inflammation	-	1 (0.1%)	1 (0.1%)
Mucosal pain	-	1 (0.1%)	1 (0.1%)
Mucosal ulceration	-	1 (0.1%)	1 (0.1%)
Multiple organ dysfunction syndrome	1 (0.1%)	-	1 (0.1%)
Oedema	20 (2.3%)	18 (2.5%)	38 (2.4%)
Oedema peripheral	31 (3.5%)	20 (2.8%)	51 (3.2%)
Pain	9 (1.0%)	2 (0.3%)	11 (0.7%)
Peripheral swelling	5 (0.6%)	3 (0.4%)	8 (0.5%)
Polyp	1 (0.1%)	-	1 (0.1%)
Pyrexia	-	1 (0.1%)	1 (0.1%)
Sensation of foreign body	1 (0.1%)	-	1 (0.1%)
Hepatobiliary disorders	9 (1.0%)	-	9 (0.6%)
Hepatic failure	1 (0.1%)	-	1 (0.1%)
Hepatotoxicity	2 (0.2%)	-	2 (0.1%)
Hyperbilirubinaemia	3 (0.3%)	-	3 (0.2%)
Jaundice	1 (0.1%)	-	1 (0.1%)
Ocular icterus	2 (0.2%)	-	2 (0.1%)
Immune system disorders	3 (0.3%)	3 (0.4%)	6 (0.4%)
Engraftment syndrome	1 (0.1%)	-	1 (0.1%)

Number of events (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Hypersensitivity	2 (0.2%)	3 (0.4%)	5 (0.3%)
Infections and infestations	51 (5.8%)	34 (4.8%)	85 (5.4%)
Atypical pneumonia	1 (0.1%)	-	1 (0.1%)
Bacterial infection	1 (0.1%)	1 (0.1%)	2 (0.1%)
Bacterial sepsis	2 (0.2%)	-	2 (0.1%)
Bronchitis	1 (0.1%)	-	1 (0.1%)
Candida infection	-	1 (0.1%)	1 (0.1%)
Catheter site abscess	1 (0.1%)	-	1 (0.1%)
Catheter site infection	-	1 (0.1%)	1 (0.1%)
Cellulitis orbital	1 (0.1%)	-	1 (0.1%)
Conjunctivitis	3 (0.3%)	2 (0.3%)	5 (0.3%)
Corynebacterium bacteraemia	2 (0.2%)	-	2 (0.1%)
Cystitis	-	1 (0.1%)	1 (0.1%)
Cytomegalovirus gastroenteritis	1 (0.1%)	-	1 (0.1%)
Cytomegalovirus infection	3 (0.3%)	-	3 (0.2%)
Cytomegalovirus viraemia	1 (0.1%)	-	1 (0.1%)
Enterococcal infection	4 (0.5%)	2 (0.3%)	6 (0.4%)
Escherichia sepsis	1 (0.1%)	-	1 (0.1%)
Genital infection fungal	-	1 (0.1%)	1 (0.1%)
Herpes simplex	1 (0.1%)	-	1 (0.1%)
Herpes virus infection	2 (0.2%)	-	2 (0.1%)
Intestinal sepsis	-	1 (0.1%)	1 (0.1%)
Listeriosis	-	1 (0.1%)	1 (0.1%)
Micrococcal sepsis	1 (0.1%)	-	1 (0.1%)
Oral herpes	2 (0.2%)	1 (0.1%)	3 (0.2%)
Parainfluenzae virus infection	1 (0.1%)	-	1 (0.1%)
Paronychia	-	1 (0.1%)	1 (0.1%)
Pneumonia	2 (0.2%)	2 (0.3%)	4 (0.3%)
Pneumonia fungal	2 (0.2%)	2 (0.3%)	4 (0.3%)
Pseudomonas infection	1 (0.1%)	1 (0.1%)	2 (0.1%)
Rash pustular	3 (0.3%)	1 (0.1%)	4 (0.3%)
Rhinitis	2 (0.2%)	3 (0.4%)	5 (0.3%)
Sepsis	5 (0.6%)	3 (0.4%)	8 (0.5%)
Septic shock	-	1 (0.1%)	1 (0.1%)
Sinusitis	1 (0.1%)	1 (0.1%)	2 (0.1%)
Sphingomonas paucimobilis infection	-	1 (0.1%)	1 (0.1%)
Staphylococcal bacteraemia	-	1 (0.1%)	1 (0.1%)
Staphylococcal infection	3 (0.3%)	1 (0.1%)	4 (0.3%)
Stenotrophomonas infection	-	2 (0.3%)	2 (0.1%)
Viral haemorrhagic cystitis	-	1 (0.1%)	1 (0.1%)
Viral infection	2 (0.2%)	-	2 (0.1%)
Viral upper respiratory tract infection	1 (0.1%)	1 (0.1%)	2 (0.1%)
Injury, poisoning and procedural complications	8 (0.9%)	4 (0.6%)	12 (0.8%)
Anal injury	1 (0.1%)	-	1 (0.1%)
Joint injury	1 (0.1%)	-	1 (0.1%)

Number of events (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Limb injury	1 (0.1%)	-	1 (0.1%)
Post procedural haemorrhage	1 (0.1%)	-	1 (0.1%)
Procedural dizziness	1 (0.1%)	-	1 (0.1%)
Scratch	-	1 (0.1%)	1 (0.1%)
Spinal fracture	1 (0.1%)	-	1 (0.1%)
Sternal fracture	-	1 (0.1%)	1 (0.1%)
Subdural haematoma	1 (0.1%)	-	1 (0.1%)
Thermal burn	-	1 (0.1%)	1 (0.1%)
Transplant failure	-	1 (0.1%)	1 (0.1%)
Vascular access site pain	1 (0.1%)	-	1 (0.1%)
Investigations	83 (9.5%)	48 (6.8%)	131 (8.3%)
Alanine aminotransferase increased	-	1 (0.1%)	1 (0.1%)
Aspartate aminotransferase increased	-	1 (0.1%)	1 (0.1%)
Blood bilirubin increased	3 (0.3%)	1 (0.1%)	4 (0.3%)
Blood creatinine increased	1 (0.1%)	1 (0.1%)	2 (0.1%)
Blood glucose increased	7 (0.8%)	3 (0.4%)	10 (0.6%)
Blood lactic acid increased	1 (0.1%)	-	1 (0.1%)
Blood pH decreased	1 (0.1%)	-	1 (0.1%)
Blood potassium decreased	2 (0.2%)	-	2 (0.1%)
Blood pressure abnormal	-	1 (0.1%)	1 (0.1%)
C-reactive protein increased	1 (0.1%)	-	1 (0.1%)
Coagulation factor XIII level decreased	-	1 (0.1%)	1 (0.1%)
Coagulation factor decreased	1 (0.1%)	-	1 (0.1%)
Enterococcus test positive	-	1 (0.1%)	1 (0.1%)
Gamma-glutamyltransferase increased	1 (0.1%)	-	1 (0.1%)
General physical condition abnormal	1 (0.1%)	-	1 (0.1%)
Hepatic enzyme increased	1 (0.1%)	-	1 (0.1%)
Immunoglobulins decreased	-	1 (0.1%)	1 (0.1%)
Inflammatory marker increased	2 (0.2%)	2 (0.3%)	4 (0.3%)
International normalised ratio increased	-	1 (0.1%)	1 (0.1%)
Lipase increased	1 (0.1%)	-	1 (0.1%)
Oxygen saturation decreased	4 (0.5%)	-	4 (0.3%)
Pancreatic enzymes decreased	1 (0.1%)	-	1 (0.1%)
Polyomavirus test positive	1 (0.1%)	-	1 (0.1%)
Pulmonary function test abnormal	-	1 (0.1%)	1 (0.1%)
Roseolovirus test positive	-	1 (0.1%)	1 (0.1%)
Transaminases increased	9 (1.0%)	1 (0.1%)	10 (0.6%)
Urine lactic acid increased	-	2 (0.3%)	2 (0.1%)
Viral titre increased	1 (0.1%)	-	1 (0.1%)
Vital capacity decreased	-	1 (0.1%)	1 (0.1%)
Weight decreased	2 (0.2%)	-	2 (0.1%)
Weight increased	39 (4.5%)	27 (3.8%)	66 (4.2%)
White blood cell count decreased	1 (0.1%)	1 (0.1%)	2 (0.1%)
pH urine decreased	2 (0.2%)	-	2 (0.1%)
Metabolism and nutrition disorders	35 (4.0%)	29 (4.1%)	64 (4.0%)
Acidosis	-	1 (0.1%)	1 (0.1%)

Number of events (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Decreased appetite	17 (1.9%)	15 (2.1%)	32 (2.0%)
Dehydration	1 (0.1%)	-	1 (0.1%)
Fluid overload	1 (0.1%)	-	1 (0.1%)
Hyperglycaemia	3 (0.3%)	4 (0.6%)	7 (0.4%)
Hyperkalaemia	-	1 (0.1%)	1 (0.1%)
Hypernatraemia	-	1 (0.1%)	1 (0.1%)
Hyperuricaemia	1 (0.1%)	-	1 (0.1%)
Hypervolaemia	1 (0.1%)	-	1 (0.1%)
Hypocalcaemia	-	2 (0.3%)	2 (0.1%)
Hypoglycaemia	1 (0.1%)	-	1 (0.1%)
Hypokalaemia	2 (0.2%)	2 (0.3%)	4 (0.3%)
Hypomagnesaemia	2 (0.2%)	2 (0.3%)	4 (0.3%)
Hyponatraemia	1 (0.1%)	1 (0.1%)	2 (0.1%)
Hypophosphataemia	1 (0.1%)	-	1 (0.1%)
Malnutrition	1 (0.1%)	-	1 (0.1%)
Polydipsia	1 (0.1%)	-	1 (0.1%)
Tumour lysis syndrome	1 (0.1%)	-	1 (0.1%)
Vitamin K deficiency	1 (0.1%)	-	1 (0.1%)
Musculoskeletal and connective tissue disorders	50 (5.7%)	41 (5.8%)	91 (5.7%)
Arthralgia	5 (0.6%)	4 (0.6%)	9 (0.6%)
Back pain	16 (1.8%)	9 (1.3%)	25 (1.6%)
Bone pain	6 (0.7%)	3 (0.4%)	9 (0.6%)
Coccydynia	1 (0.1%)	-	1 (0.1%)
Flank pain	1 (0.1%)	2 (0.3%)	3 (0.2%)
Groin pain	2 (0.2%)	-	2 (0.1%)
Jaw cyst	-	1 (0.1%)	1 (0.1%)
Limb discomfort	1 (0.1%)	-	1 (0.1%)
Muscle spasms	1 (0.1%)	3 (0.4%)	4 (0.3%)
Muscle tightness	-	1 (0.1%)	1 (0.1%)
Muscular weakness	-	1 (0.1%)	1 (0.1%)
Musculoskeletal disorder	-	1 (0.1%)	1 (0.1%)
Musculoskeletal pain	4 (0.5%)	4 (0.6%)	8 (0.5%)
Myosclerosis	-	1 (0.1%)	1 (0.1%)
Neck pain	3 (0.3%)	4 (0.6%)	7 (0.4%)
Pain in extremity	7 (0.8%)	4 (0.6%)	11 (0.7%)
Pain in jaw	1 (0.1%)	-	1 (0.1%)
Plantar fasciitis	1 (0.1%)	-	1 (0.1%)
Sjogren's syndrome	-	2 (0.3%)	2 (0.1%)
Spinal pain	1 (0.1%)	-	1 (0.1%)
Tendon disorder	-	1 (0.1%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl	3 (0.3%)	-	3 (0.2%)
Acute myeloid leukaemia	2 (0.2%)	-	2 (0.1%)
Skin papilloma	1 (0.1%)	-	1 (0.1%)
Nervous system disorders	64 (7.3%)	53 (7.5%)	117 (7.4%)

Number of events (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Aphasia	-	1 (0.1%)	1 (0.1%)
Burning sensation	1 (0.1%)	1 (0.1%)	2 (0.1%)
Coma	-	1 (0.1%)	1 (0.1%)
Depressed level of consciousness	1 (0.1%)	-	1 (0.1%)
Dizziness	14 (1.6%)	14 (2.0%)	28 (1.8%)
Dysarthria	-	1 (0.1%)	1 (0.1%)
Headache	32 (3.7%)	20 (2.8%)	52 (3.3%)
Hyperaesthesia	1 (0.1%)	-	1 (0.1%)
Hypoaesthesia	-	1 (0.1%)	1 (0.1%)
Orthostatic intolerance	-	1 (0.1%)	1 (0.1%)
Paraesthesia	3 (0.3%)	6 (0.8%)	9 (0.6%)
Polyneuropathy	4 (0.5%)	-	4 (0.3%)
Seizure	1 (0.1%)	-	1 (0.1%)
Somnolence	1 (0.1%)	1 (0.1%)	2 (0.1%)
Syncope	1 (0.1%)	1 (0.1%)	2 (0.1%)
Tremor	4 (0.5%)	5 (0.7%)	9 (0.6%)
VIth nerve disorder	1 (0.1%)	-	1 (0.1%)
Psychiatric disorders	38 (4.3%)	26 (3.7%)	64 (4.0%)
Agitation	1 (0.1%)	1 (0.1%)	2 (0.1%)
Anorexia and bulimia syndrome	2 (0.2%)	-	2 (0.1%)
Anxiety	4 (0.5%)	1 (0.1%)	5 (0.3%)
Confusional state	2 (0.2%)	1 (0.1%)	3 (0.2%)
Delirium	1 (0.1%)	-	1 (0.1%)
Depression	2 (0.2%)	3 (0.4%)	5 (0.3%)
Hallucination	3 (0.3%)	1 (0.1%)	4 (0.3%)
Hallucination, visual	-	1 (0.1%)	1 (0.1%)
Insomnia	14 (1.6%)	13 (1.8%)	27 (1.7%)
Mental disorder	1 (0.1%)	-	1 (0.1%)
Nightmare	2 (0.2%)	-	2 (0.1%)
Psychiatric symptom	-	1 (0.1%)	1 (0.1%)
Restlessness	1 (0.1%)	3 (0.4%)	4 (0.3%)
Sleep disorder	3 (0.3%)	-	3 (0.2%)
Sopor	-	1 (0.1%)	1 (0.1%)
Tension	2 (0.2%)	-	2 (0.1%)
Renal and urinary disorders	27 (3.1%)	24 (3.4%)	51 (3.2%)
Acute kidney injury	3 (0.3%)	4 (0.6%)	7 (0.4%)
Azotaemia	-	1 (0.1%)	1 (0.1%)
Chromaturia	3 (0.3%)	-	3 (0.2%)
Dysuria	5 (0.6%)	7 (1.0%)	12 (0.8%)
Haematuria	2 (0.2%)	3 (0.4%)	5 (0.3%)
Nocturia	3 (0.3%)	3 (0.4%)	6 (0.4%)
Oliguria	1 (0.1%)	1 (0.1%)	2 (0.1%)
Pollakiuria	4 (0.5%)	-	4 (0.3%)
Polyuria	2 (0.2%)	-	2 (0.1%)
Renal failure	1 (0.1%)	3 (0.4%)	4 (0.3%)
Renal impairment	2 (0.2%)	-	2 (0.1%)

Number of events (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Renal pain	-	1 (0.1%)	1 (0.1%)
Urinary retention	-	1 (0.1%)	1 (0.1%)
Urinary tract pain	1 (0.1%)	-	1 (0.1%)
Reproductive system and breast disorders	3 (0.3%)	7 (1.0%)	10 (0.6%)
Breast pain	-	1 (0.1%)	1 (0.1%)
Dysmenorrhoea	-	1 (0.1%)	1 (0.1%)
Genital blister	-	1 (0.1%)	1 (0.1%)
Genital rash	1 (0.1%)	-	1 (0.1%)
Genital swelling	-	1 (0.1%)	1 (0.1%)
Menstrual discomfort	-	1 (0.1%)	1 (0.1%)
Pelvic pain	1 (0.1%)	1 (0.1%)	2 (0.1%)
Vulvovaginal burning sensation	-	1 (0.1%)	1 (0.1%)
Vulvovaginal pruritus	1 (0.1%)	-	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	54 (6.2%)	38 (5.3%)	92 (5.8%)
Atelectasis	2 (0.2%)	-	2 (0.1%)
Cough	15 (1.7%)	6 (0.8%)	21 (1.3%)
Dysphonia	2 (0.2%)	2 (0.3%)	4 (0.3%)
Dyspnoea	7 (0.8%)	9 (1.3%)	16 (1.0%)
Dyspnoea exertional	3 (0.3%)	3 (0.4%)	6 (0.4%)
Epistaxis	-	1 (0.1%)	1 (0.1%)
Haemoptysis	-	1 (0.1%)	1 (0.1%)
Hiccups	4 (0.5%)	2 (0.3%)	6 (0.4%)
Hypoxia	3 (0.3%)	2 (0.3%)	5 (0.3%)
Laryngeal pain	1 (0.1%)	-	1 (0.1%)
Nasal discomfort	1 (0.1%)	-	1 (0.1%)
Nasal dryness	2 (0.2%)	-	2 (0.1%)
Oropharyngeal pain	3 (0.3%)	5 (0.7%)	8 (0.5%)
Orthopnoea	-	1 (0.1%)	1 (0.1%)
Pharyngeal erythema	1 (0.1%)	-	1 (0.1%)
Pleural effusion	4 (0.5%)	2 (0.3%)	6 (0.4%)
Productive cough	1 (0.1%)	-	1 (0.1%)
Pulmonary congestion	1 (0.1%)	-	1 (0.1%)
Pulmonary oedema	-	1 (0.1%)	1 (0.1%)
Respiratory failure	1 (0.1%)	2 (0.3%)	3 (0.2%)
Rhinorrhoea	1 (0.1%)	1 (0.1%)	2 (0.1%)
Sneezing	1 (0.1%)	-	1 (0.1%)
Tachypnoea	1 (0.1%)	-	1 (0.1%)
Skin and subcutaneous tissue disorders	89 (10.2%)	64 (9.0%)	153 (9.7%)
Blister	1 (0.1%)	3 (0.4%)	4 (0.3%)
Blood blister	1 (0.1%)	-	1 (0.1%)
Cold sweat	1 (0.1%)	1 (0.1%)	2 (0.1%)
Decubitus ulcer	1 (0.1%)	-	1 (0.1%)
Dermatitis	-	1 (0.1%)	1 (0.1%)
Dry skin	12 (1.4%)	2 (0.3%)	14 (0.9%)
Erythema	9 (1.0%)	4 (0.6%)	13 (0.8%)

Number of events (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Hyperhidrosis	3 (0.3%)	2 (0.3%)	5 (0.3%)
Nail disorder	1 (0.1%)	-	1 (0.1%)
Night sweats	3 (0.3%)	-	3 (0.2%)
Pain of skin	1 (0.1%)	-	1 (0.1%)
Palmar erythema	-	1 (0.1%)	1 (0.1%)
Palmar-plantar erythrodysaesthesia syndrome	9 (1.0%)	8 (1.1%)	17 (1.1%)
Pruritus	20 (2.3%)	8 (1.1%)	28 (1.8%)
Purpura	-	1 (0.1%)	1 (0.1%)
Rash	22 (2.5%)	26 (3.7%)	48 (3.0%)
Rash maculo-papular	1 (0.1%)	-	1 (0.1%)
Rash pruritic	-	1 (0.1%)	1 (0.1%)
Skin exfoliation	2 (0.2%)	2 (0.3%)	4 (0.3%)
Skin fissures	-	1 (0.1%)	1 (0.1%)
Skin lesion	1 (0.1%)	1 (0.1%)	2 (0.1%)
Skin maceration	-	1 (0.1%)	1 (0.1%)
Swelling face	1 (0.1%)	1 (0.1%)	2 (0.1%)
Vascular disorders	30 (3.4%)	23 (3.2%)	53 (3.3%)
Circulatory collapse	-	1 (0.1%)	1 (0.1%)
Extremity necrosis	-	1 (0.1%)	1 (0.1%)
Flushing	4 (0.5%)	4 (0.6%)	8 (0.5%)
Haematoma	1 (0.1%)	-	1 (0.1%)
Hot flush	3 (0.3%)	-	3 (0.2%)
Hypertension	8 (0.9%)	7 (1.0%)	15 (0.9%)
Hypotension	12 (1.4%)	7 (1.0%)	19 (1.2%)
Pallor	-	1 (0.1%)	1 (0.1%)
Peripheral coldness	1 (0.1%)	-	1 (0.1%)
Thrombophlebitis	-	1 (0.1%)	1 (0.1%)
Venoocclusive disease	1 (0.1%)	1 (0.1%)	2 (0.1%)

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

Number of patients (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Number of patients with at least one AE	30 (100.0%)	30 (100.0%)	60 (100.0%)
Blood and lymphatic system disorders	3 (10.0%)	3 (10.0%)	6 (10.0%)
Coagulopathy	1 (3.3%)	-	1 (1.7%)
Febrile neutropenia	-	1 (3.3%)	1 (1.7%)
Hilar lymphadenopathy	1 (3.3%)	-	1 (1.7%)
Lymphadenopathy	-	1 (3.3%)	1 (1.7%)
Splenomegaly	2 (6.7%)	-	2 (3.3%)
Thrombotic thrombocytopenic purpura	-	1 (3.3%)	1 (1.7%)
Cardiac disorders	2 (6.7%)	7 (23.3%)	9 (15.0%)
Bradycardia	1 (3.3%)	-	1 (1.7%)
Cardiomegaly	-	1 (3.3%)	1 (1.7%)
Cardiovascular insufficiency	-	1 (3.3%)	1 (1.7%)
Cyanosis	-	1 (3.3%)	1 (1.7%)
Pericardial effusion	-	1 (3.3%)	1 (1.7%)
Sinus bradycardia	1 (3.3%)	-	1 (1.7%)
Sinus tachycardia	-	1 (3.3%)	1 (1.7%)
Tachycardia	1 (3.3%)	2 (6.7%)	3 (5.0%)
Ventricular tachycardia	-	1 (3.3%)	1 (1.7%)
Ear and labyrinth disorders	8 (26.7%)	5 (16.7%)	13 (21.7%)
Deafness neurosensory	1 (3.3%)	-	1 (1.7%)
Hypoacusis	-	2 (6.7%)	2 (3.3%)
Middle ear effusion	1 (3.3%)	-	1 (1.7%)
Vertigo	6 (20.0%)	4 (13.3%)	10 (16.7%)
Endocrine disorders	1 (3.3%)	2 (6.7%)	3 (5.0%)
Adrenal disorder	-	1 (3.3%)	1 (1.7%)
Hyperthyroidism	1 (3.3%)	1 (3.3%)	2 (3.3%)
Eye disorders	10 (33.3%)	10 (33.3%)	20 (33.3%)
Conjunctival oedema	1 (3.3%)	-	1 (1.7%)
Dry eye	3 (10.0%)	3 (10.0%)	6 (10.0%)
Eye haemorrhage	-	1 (3.3%)	1 (1.7%)
Eye irritation	1 (3.3%)	1 (3.3%)	2 (3.3%)
Eyelid oedema	2 (6.7%)	3 (10.0%)	5 (8.3%)
Lacrimation increased	2 (6.7%)	1 (3.3%)	3 (5.0%)
Ocular discomfort	1 (3.3%)	-	1 (1.7%)
Ocular hyperaemia	2 (6.7%)	-	2 (3.3%)
Photopsia	-	1 (3.3%)	1 (1.7%)
Vision blurred	1 (3.3%)	-	1 (1.7%)
Visual impairment	-	1 (3.3%)	1 (1.7%)
Vitreous haemorrhage	-	1 (3.3%)	1 (1.7%)
Gastrointestinal disorders	28 (93.3%)	30 (100.0%)	58 (96.7%)
Abdominal discomfort	4 (13.3%)	4 (13.3%)	8 (13.3%)

Number of patients (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Abdominal distension	1 (3.3%)	2 (6.7%)	3 (5.0%)
Abdominal pain	12 (40.0%)	10 (33.3%)	22 (36.7%)
Abdominal pain upper	8 (26.7%)	12 (40.0%)	20 (33.3%)
Anorectal disorder	1 (3.3%)	-	1 (1.7%)
Aphthous ulcer	1 (3.3%)	-	1 (1.7%)
Ascites	1 (3.3%)	-	1 (1.7%)
Coating in mouth	-	1 (3.3%)	1 (1.7%)
Constipation	16 (53.3%)	13 (43.3%)	29 (48.3%)
Diarrhoea	22 (73.3%)	22 (73.3%)	44 (73.3%)
Dry mouth	2 (6.7%)	1 (3.3%)	3 (5.0%)
Dyspepsia	1 (3.3%)	6 (20.0%)	7 (11.7%)
Dysphagia	2 (6.7%)	2 (6.7%)	4 (6.7%)
Enteritis	-	1 (3.3%)	1 (1.7%)
Epigastric discomfort	-	1 (3.3%)	1 (1.7%)
Eructation	1 (3.3%)	-	1 (1.7%)
Flatulence	3 (10.0%)	2 (6.7%)	5 (8.3%)
Gastric disorder	-	1 (3.3%)	1 (1.7%)
Gastritis	1 (3.3%)	-	1 (1.7%)
Gastrooesophageal reflux disease	3 (10.0%)	2 (6.7%)	5 (8.3%)
Haemorrhoids	4 (13.3%)	2 (6.7%)	6 (10.0%)
Impaired gastric emptying	1 (3.3%)	-	1 (1.7%)
Lip blister	-	1 (3.3%)	1 (1.7%)
Lip pruritus	-	1 (3.3%)	1 (1.7%)
Lip swelling	-	1 (3.3%)	1 (1.7%)
Melaena	1 (3.3%)	-	1 (1.7%)
Mouth haemorrhage	-	1 (3.3%)	1 (1.7%)
Mouth swelling	2 (6.7%)	-	2 (3.3%)
Mouth ulceration	1 (3.3%)	-	1 (1.7%)
Nausea	-	2 (6.7%)	2 (3.3%)
Odynophagia	1 (3.3%)	1 (3.3%)	2 (3.3%)
Oesophageal pain	1 (3.3%)	1 (3.3%)	2 (3.3%)
Oesophagitis	1 (3.3%)	1 (3.3%)	2 (3.3%)
Oral discomfort	3 (10.0%)	1 (3.3%)	4 (6.7%)
Oral mucosal blistering	1 (3.3%)	1 (3.3%)	2 (3.3%)
Oral mucosal erythema	2 (6.7%)	-	2 (3.3%)
Oral pain	-	1 (3.3%)	1 (1.7%)
Pancreatitis	1 (3.3%)	-	1 (1.7%)
Proctalgia	1 (3.3%)	-	1 (1.7%)
Small intestinal obstruction	-	1 (3.3%)	1 (1.7%)
Stomatitis	-	1 (3.3%)	1 (1.7%)
Tongue coated	1 (3.3%)	1 (3.3%)	2 (3.3%)
Tongue ulceration	-	2 (6.7%)	2 (3.3%)
Toothache	-	1 (3.3%)	1 (1.7%)
Vomiting	-	2 (6.7%)	2 (3.3%)
General disorders and administration site conditio	30 (100.0%)	29 (96.7%)	59 (98.3%)
Administration site papule	1 (3.3%)	-	1 (1.7%)

Number of patients (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Asthenia	2 (6.7%)	1 (3.3%)	3 (5.0%)
Axillary pain	1 (3.3%)	1 (3.3%)	2 (3.3%)
Catheter site erythema	3 (10.0%)	5 (16.7%)	8 (13.3%)
Catheter site haematoma	1 (3.3%)	2 (6.7%)	3 (5.0%)
Catheter site haemorrhage	2 (6.7%)	2 (6.7%)	4 (6.7%)
Catheter site inflammation	-	1 (3.3%)	1 (1.7%)
Catheter site pain	5 (16.7%)	6 (20.0%)	11 (18.3%)
Catheter site related reaction	-	2 (6.7%)	2 (3.3%)
Catheter site swelling	1 (3.3%)	4 (13.3%)	5 (8.3%)
Chest discomfort	2 (6.7%)	1 (3.3%)	3 (5.0%)
Chest pain	7 (23.3%)	5 (16.7%)	12 (20.0%)
Chills	12 (40.0%)	18 (60.0%)	30 (50.0%)
Disease progression	1 (3.3%)	-	1 (1.7%)
Early satiety	-	1 (3.3%)	1 (1.7%)
Face oedema	2 (6.7%)	1 (3.3%)	3 (5.0%)
Facial pain	-	1 (3.3%)	1 (1.7%)
Fatigue	24 (80.0%)	18 (60.0%)	42 (70.0%)
Feeling hot	2 (6.7%)	1 (3.3%)	3 (5.0%)
Gait disturbance	2 (6.7%)	-	2 (3.3%)
Injection site extravasation	1 (3.3%)	-	1 (1.7%)
Injection site reaction	1 (3.3%)	-	1 (1.7%)
Malaise	2 (6.7%)	1 (3.3%)	3 (5.0%)
Mucosal dryness	1 (3.3%)	1 (3.3%)	2 (3.3%)
Mucosal haemorrhage	-	1 (3.3%)	1 (1.7%)
Mucosal inflammation	-	1 (3.3%)	1 (1.7%)
Mucosal pain	-	1 (3.3%)	1 (1.7%)
Mucosal ulceration	-	1 (3.3%)	1 (1.7%)
Multiple organ dysfunction syndrome	1 (3.3%)	-	1 (1.7%)
Oedema	15 (50.0%)	11 (36.7%)	26 (43.3%)
Oedema peripheral	14 (46.7%)	13 (43.3%)	27 (45.0%)
Pain	8 (26.7%)	2 (6.7%)	10 (16.7%)
Peripheral swelling	4 (13.3%)	1 (3.3%)	5 (8.3%)
Polyp	1 (3.3%)	-	1 (1.7%)
Pyrexia	-	1 (3.3%)	1 (1.7%)
Sensation of foreign body	1 (3.3%)	-	1 (1.7%)
Hepatobiliary disorders	6 (20.0%)	-	6 (10.0%)
Hepatic failure	1 (3.3%)	-	1 (1.7%)
Hepatotoxicity	2 (6.7%)	-	2 (3.3%)
Hyperbilirubinaemia	2 (6.7%)	-	2 (3.3%)
Jaundice	1 (3.3%)	-	1 (1.7%)
Ocular icterus	2 (6.7%)	-	2 (3.3%)
Immune system disorders	3 (10.0%)	2 (6.7%)	5 (8.3%)
Engraftment syndrome	1 (3.3%)	-	1 (1.7%)
Hypersensitivity	2 (6.7%)	2 (6.7%)	4 (6.7%)
Infections and infestations	17 (56.7%)	15 (50.0%)	32 (53.3%)

Number of patients (General AE)

	Treatment arm - CODELIST		
System Organ Class Preferred Term	ClAraC N=30	FLAMSA N=30	Total N=60
Atypical pneumonia	1 (3.3%)	-	1 (1.7%)
Bacterial infection	1 (3.3%)	1 (3.3%)	2 (3.3%)
Bacterial sepsis	1 (3.3%)	-	1 (1.7%)
Bronchitis	1 (3.3%)	-	1 (1.7%)
Candida infection	-	1 (3.3%)	1 (1.7%)
Catheter site abscess	1 (3.3%)	-	1 (1.7%)
Catheter site infection	-	1 (3.3%)	1 (1.7%)
Cellulitis orbital	1 (3.3%)	-	1 (1.7%)
Conjunctivitis	3 (10.0%)	2 (6.7%)	5 (8.3%)
Corynebacterium bacteraemia	2 (6.7%)	-	2 (3.3%)
Cystitis	-	1 (3.3%)	1 (1.7%)
Cytomegalovirus gastroenteritis	1 (3.3%)	-	1 (1.7%)
Cytomegalovirus infection	3 (10.0%)	-	3 (5.0%)
Cytomegalovirus viraemia	1 (3.3%)	-	1 (1.7%)
Enterococcal infection	3 (10.0%)	2 (6.7%)	5 (8.3%)
Escherichia sepsis	1 (3.3%)	-	1 (1.7%)
Genital infection fungal	-	1 (3.3%)	1 (1.7%)
Herpes simplex	1 (3.3%)	-	1 (1.7%)
Herpes virus infection	2 (6.7%)	-	2 (3.3%)
Intestinal sepsis	-	1 (3.3%)	1 (1.7%)
Listeriosis	-	1 (3.3%)	1 (1.7%)
Micrococcal sepsis	1 (3.3%)	-	1 (1.7%)
Oral herpes	2 (6.7%)	1 (3.3%)	3 (5.0%)
Parainfluenzae virus infection	1 (3.3%)	-	1 (1.7%)
Paronychia	-	1 (3.3%)	1 (1.7%)
Pneumonia	2 (6.7%)	2 (6.7%)	4 (6.7%)
Pneumonia fungal	2 (6.7%)	2 (6.7%)	4 (6.7%)
Pseudomonas infection	1 (3.3%)	1 (3.3%)	2 (3.3%)
Rash pustular	3 (10.0%)	1 (3.3%)	4 (6.7%)
Rhinitis	1 (3.3%)	3 (10.0%)	4 (6.7%)
Sepsis	5 (16.7%)	3 (10.0%)	8 (13.3%)
Septic shock	-	1 (3.3%)	1 (1.7%)
Sinusitis	1 (3.3%)	1 (3.3%)	2 (3.3%)
Sphingomonas paucimobilis infection	-	1 (3.3%)	1 (1.7%)
Staphylococcal bacteraemia	-	1 (3.3%)	1 (1.7%)
Staphylococcal infection	3 (10.0%)	1 (3.3%)	4 (6.7%)
Stenotrophomonas infection	-	2 (6.7%)	2 (3.3%)
Viral haemorrhagic cystitis	-	1 (3.3%)	1 (1.7%)
Viral infection	1 (3.3%)	-	1 (1.7%)
Viral upper respiratory tract infection	1 (3.3%)	1 (3.3%)	2 (3.3%)
Injury, poisoning and procedural complications	5 (16.7%)	3 (10.0%)	8 (13.3%)
Anal injury	1 (3.3%)	-	1 (1.7%)
Joint injury	1 (3.3%)	-	1 (1.7%)
Limb injury	1 (3.3%)	-	1 (1.7%)
Post procedural haemorrhage	1 (3.3%)	-	1 (1.7%)
Procedural dizziness	1 (3.3%)	-	1 (1.7%)

Number of patients (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Scratch	-	1 (3.3%)	1 (1.7%)
Spinal fracture	1 (3.3%)	-	1 (1.7%)
Sternal fracture	-	1 (3.3%)	1 (1.7%)
Subdural haematoma	1 (3.3%)	-	1 (1.7%)
Thermal burn	-	1 (3.3%)	1 (1.7%)
Transplant failure	-	1 (3.3%)	1 (1.7%)
Vascular access site pain	1 (3.3%)	-	1 (1.7%)
Investigations	27 (90.0%)	23 (76.7%)	50 (83.3%)
Alanine aminotransferase increased	-	1 (3.3%)	1 (1.7%)
Aspartate aminotransferase increased	-	1 (3.3%)	1 (1.7%)
Blood bilirubin increased	2 (6.7%)	1 (3.3%)	3 (5.0%)
Blood creatinine increased	1 (3.3%)	1 (3.3%)	2 (3.3%)
Blood glucose increased	3 (10.0%)	3 (10.0%)	6 (10.0%)
Blood lactic acid increased	1 (3.3%)	-	1 (1.7%)
Blood pH decreased	1 (3.3%)	-	1 (1.7%)
Blood potassium decreased	2 (6.7%)	-	2 (3.3%)
Blood pressure abnormal	-	1 (3.3%)	1 (1.7%)
C-reactive protein increased	1 (3.3%)	-	1 (1.7%)
Coagulation factor XIII level decreased	-	1 (3.3%)	1 (1.7%)
Coagulation factor decreased	1 (3.3%)	-	1 (1.7%)
Enterococcus test positive	-	1 (3.3%)	1 (1.7%)
Gamma-glutamyltransferase increased	1 (3.3%)	-	1 (1.7%)
General physical condition abnormal	1 (3.3%)	-	1 (1.7%)
Hepatic enzyme increased	1 (3.3%)	-	1 (1.7%)
Immunoglobulins decreased	-	1 (3.3%)	1 (1.7%)
Inflammatory marker increased	2 (6.7%)	2 (6.7%)	4 (6.7%)
International normalised ratio increased	-	1 (3.3%)	1 (1.7%)
Lipase increased	1 (3.3%)	-	1 (1.7%)
Oxygen saturation decreased	4 (13.3%)	-	4 (6.7%)
Pancreatic enzymes decreased	1 (3.3%)	-	1 (1.7%)
Polyomavirus test positive	1 (3.3%)	-	1 (1.7%)
Pulmonary function test abnormal	-	1 (3.3%)	1 (1.7%)
Roseolovirus test positive	-	1 (3.3%)	1 (1.7%)
Transaminases increased	8 (26.7%)	1 (3.3%)	9 (15.0%)
Urine lactic acid increased	-	2 (6.7%)	2 (3.3%)
Viral titre increased	1 (3.3%)	-	1 (1.7%)
Vital capacity decreased	-	1 (3.3%)	1 (1.7%)
Weight decreased	2 (6.7%)	-	2 (3.3%)
Weight increased	23 (76.7%)	19 (63.3%)	42 (70.0%)
White blood cell count decreased	1 (3.3%)	1 (3.3%)	2 (3.3%)
pH urine decreased	2 (6.7%)	-	2 (3.3%)
Metabolism and nutrition disorders	18 (60.0%)	19 (63.3%)	37 (61.7%)
Acidosis	-	1 (3.3%)	1 (1.7%)
Decreased appetite	12 (40.0%)	14 (46.7%)	26 (43.3%)
Dehydration	1 (3.3%)	-	1 (1.7%)
Fluid overload	1 (3.3%)	-	1 (1.7%)

Number of patients (General AE)

	Treatment arm - CODELIST		
System Organ Class Preferred Term	ClAraC N=30	FLAMSA N=30	Total N=60
Hyperglycaemia	3 (10.0%)	4 (13.3%)	7 (11.7%)
Hyperkalaemia	-	1 (3.3%)	1 (1.7%)
Hypernatraemia	-	1 (3.3%)	1 (1.7%)
Hyperuricaemia	1 (3.3%)	-	1 (1.7%)
Hypervolaemia	1 (3.3%)	-	1 (1.7%)
Hypocalcaemia	-	2 (6.7%)	2 (3.3%)
Hypoglycaemia	1 (3.3%)	-	1 (1.7%)
Hypokalaemia	2 (6.7%)	2 (6.7%)	4 (6.7%)
Hypomagnesaemia	2 (6.7%)	2 (6.7%)	4 (6.7%)
Hyponatraemia	1 (3.3%)	1 (3.3%)	2 (3.3%)
Hypophosphataemia	1 (3.3%)	-	1 (1.7%)
Malnutrition	1 (3.3%)	-	1 (1.7%)
Polydipsia	1 (3.3%)	-	1 (1.7%)
Tumour lysis syndrome	1 (3.3%)	-	1 (1.7%)
Vitamin K deficiency	1 (3.3%)	-	1 (1.7%)
Musculoskeletal and connective tissue disorders	21 (70.0%)	21 (70.0%)	42 (70.0%)
Arthralgia	4 (13.3%)	4 (13.3%)	8 (13.3%)
Back pain	10 (33.3%)	8 (26.7%)	18 (30.0%)
Bone pain	5 (16.7%)	3 (10.0%)	8 (13.3%)
Coccydynia	1 (3.3%)	-	1 (1.7%)
Flank pain	1 (3.3%)	2 (6.7%)	3 (5.0%)
Groin pain	1 (3.3%)	-	1 (1.7%)
Jaw cyst	-	1 (3.3%)	1 (1.7%)
Limb discomfort	1 (3.3%)	-	1 (1.7%)
Muscle spasms	1 (3.3%)	3 (10.0%)	4 (6.7%)
Muscle tightness	-	1 (3.3%)	1 (1.7%)
Muscular weakness	-	1 (3.3%)	1 (1.7%)
Musculoskeletal disorder	-	1 (3.3%)	1 (1.7%)
Musculoskeletal pain	4 (13.3%)	4 (13.3%)	8 (13.3%)
Myosclerosis	-	1 (3.3%)	1 (1.7%)
Neck pain	3 (10.0%)	4 (13.3%)	7 (11.7%)
Pain in extremity	7 (23.3%)	4 (13.3%)	11 (18.3%)
Pain in jaw	1 (3.3%)	-	1 (1.7%)
Plantar fasciitis	1 (3.3%)	-	1 (1.7%)
Sjogren's syndrome	-	2 (6.7%)	2 (3.3%)
Spinal pain	1 (3.3%)	-	1 (1.7%)
Tendon disorder	-	1 (3.3%)	1 (1.7%)
Neoplasms benign, malignant and unspecified (incl	3 (10.0%)	-	3 (5.0%)
Acute myeloid leukaemia	2 (6.7%)	-	2 (3.3%)
Skin papilloma	1 (3.3%)	-	1 (1.7%)
Nervous system disorders	25 (83.3%)	22 (73.3%)	47 (78.3%)
Aphasia	-	1 (3.3%)	1 (1.7%)
Burning sensation	1 (3.3%)	1 (3.3%)	2 (3.3%)
Coma	-	1 (3.3%)	1 (1.7%)

Number of patients (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Depressed level of consciousness	1 (3.3%)	-	1 (1.7%)
Dizziness	11 (36.7%)	13 (43.3%)	24 (40.0%)
Dysarthria	-	1 (3.3%)	1 (1.7%)
Headache	17 (56.7%)	13 (43.3%)	30 (50.0%)
Hyperaesthesia	1 (3.3%)	-	1 (1.7%)
Hypoaesthesia	-	1 (3.3%)	1 (1.7%)
Orthostatic intolerance	-	1 (3.3%)	1 (1.7%)
Paraesthesia	3 (10.0%)	6 (20.0%)	9 (15.0%)
Polyneuropathy	2 (6.7%)	-	2 (3.3%)
Seizure	1 (3.3%)	-	1 (1.7%)
Somnolence	1 (3.3%)	1 (3.3%)	2 (3.3%)
Syncope	1 (3.3%)	1 (3.3%)	2 (3.3%)
Tremor	3 (10.0%)	5 (16.7%)	8 (13.3%)
VIth nerve disorder	1 (3.3%)	-	1 (1.7%)
Psychiatric disorders	20 (66.7%)	18 (60.0%)	38 (63.3%)
Agitation	1 (3.3%)	1 (3.3%)	2 (3.3%)
Anorexia and bulimia syndrome	2 (6.7%)	-	2 (3.3%)
Anxiety	3 (10.0%)	1 (3.3%)	4 (6.7%)
Confusional state	2 (6.7%)	1 (3.3%)	3 (5.0%)
Delirium	1 (3.3%)	-	1 (1.7%)
Depression	2 (6.7%)	3 (10.0%)	5 (8.3%)
Hallucination	3 (10.0%)	1 (3.3%)	4 (6.7%)
Hallucination, visual	-	1 (3.3%)	1 (1.7%)
Insomnia	12 (40.0%)	11 (36.7%)	23 (38.3%)
Mental disorder	1 (3.3%)	-	1 (1.7%)
Nightmare	2 (6.7%)	-	2 (3.3%)
Psychiatric symptom	-	1 (3.3%)	1 (1.7%)
Restlessness	1 (3.3%)	2 (6.7%)	3 (5.0%)
Sleep disorder	3 (10.0%)	-	3 (5.0%)
Sopor	-	1 (3.3%)	1 (1.7%)
Tension	2 (6.7%)	-	2 (3.3%)
Renal and urinary disorders	17 (56.7%)	17 (56.7%)	34 (56.7%)
Acute kidney injury	3 (10.0%)	4 (13.3%)	7 (11.7%)
Azotaemia	-	1 (3.3%)	1 (1.7%)
Chromaturia	2 (6.7%)	-	2 (3.3%)
Dysuria	5 (16.7%)	5 (16.7%)	10 (16.7%)
Haematuria	2 (6.7%)	3 (10.0%)	5 (8.3%)
Nocturia	3 (10.0%)	3 (10.0%)	6 (10.0%)
Oliguria	1 (3.3%)	1 (3.3%)	2 (3.3%)
Pollakiuria	4 (13.3%)	-	4 (6.7%)
Polyuria	2 (6.7%)	-	2 (3.3%)
Renal failure	1 (3.3%)	3 (10.0%)	4 (6.7%)
Renal impairment	2 (6.7%)	-	2 (3.3%)
Renal pain	-	1 (3.3%)	1 (1.7%)
Urinary retention	-	1 (3.3%)	1 (1.7%)
Urinary tract pain	1 (3.3%)	-	1 (1.7%)

Number of patients (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Reproductive system and breast disorders	3 (10.0%)	6 (20.0%)	9 (15.0%)
Breast pain	-	1 (3.3%)	1 (1.7%)
Dysmenorrhoea	-	1 (3.3%)	1 (1.7%)
Genital blister	-	1 (3.3%)	1 (1.7%)
Genital rash	1 (3.3%)	-	1 (1.7%)
Genital swelling	-	1 (3.3%)	1 (1.7%)
Menstrual discomfort	-	1 (3.3%)	1 (1.7%)
Pelvic pain	1 (3.3%)	1 (3.3%)	2 (3.3%)
Vulvovaginal burning sensation	-	1 (3.3%)	1 (1.7%)
Vulvovaginal pruritus	1 (3.3%)	-	1 (1.7%)
Respiratory, thoracic and mediastinal disorders	22 (73.3%)	15 (50.0%)	37 (61.7%)
Atelectasis	2 (6.7%)	-	2 (3.3%)
Cough	9 (30.0%)	5 (16.7%)	14 (23.3%)
Dysphonia	2 (6.7%)	2 (6.7%)	4 (6.7%)
Dyspnoea	7 (23.3%)	6 (20.0%)	13 (21.7%)
Dyspnoea exertional	3 (10.0%)	2 (6.7%)	5 (8.3%)
Epistaxis	-	1 (3.3%)	1 (1.7%)
Haemoptysis	-	1 (3.3%)	1 (1.7%)
Hiccups	4 (13.3%)	2 (6.7%)	6 (10.0%)
Hypoxia	3 (10.0%)	1 (3.3%)	4 (6.7%)
Laryngeal pain	1 (3.3%)	-	1 (1.7%)
Nasal discomfort	1 (3.3%)	-	1 (1.7%)
Nasal dryness	2 (6.7%)	-	2 (3.3%)
Oropharyngeal pain	3 (10.0%)	5 (16.7%)	8 (13.3%)
Orthopnoea	-	1 (3.3%)	1 (1.7%)
Pharyngeal erythema	1 (3.3%)	-	1 (1.7%)
Pleural effusion	3 (10.0%)	2 (6.7%)	5 (8.3%)
Productive cough	1 (3.3%)	-	1 (1.7%)
Pulmonary congestion	1 (3.3%)	-	1 (1.7%)
Pulmonary oedema	-	1 (3.3%)	1 (1.7%)
Respiratory failure	1 (3.3%)	2 (6.7%)	3 (5.0%)
Rhinorrhoea	1 (3.3%)	1 (3.3%)	2 (3.3%)
Sneezing	1 (3.3%)	-	1 (1.7%)
Tachypnoea	1 (3.3%)	-	1 (1.7%)
Skin and subcutaneous tissue disorders	24 (80.0%)	24 (80.0%)	48 (80.0%)
Blister	1 (3.3%)	2 (6.7%)	3 (5.0%)
Blood blister	1 (3.3%)	-	1 (1.7%)
Cold sweat	1 (3.3%)	1 (3.3%)	2 (3.3%)
Decubitus ulcer	1 (3.3%)	-	1 (1.7%)
Dermatitis	-	1 (3.3%)	1 (1.7%)
Dry skin	9 (30.0%)	1 (3.3%)	10 (16.7%)
Erythema	8 (26.7%)	4 (13.3%)	12 (20.0%)
Hyperhidrosis	3 (10.0%)	2 (6.7%)	5 (8.3%)
Nail disorder	1 (3.3%)	-	1 (1.7%)
Night sweats	3 (10.0%)	-	3 (5.0%)

Number of patients (General AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Pain of skin	1 (3.3%)	-	1 (1.7%)
Palmar erythema	-	1 (3.3%)	1 (1.7%)
Palmar-plantar erythrodysaesthesia syndrome	9 (30.0%)	8 (26.7%)	17 (28.3%)
Pruritus	10 (33.3%)	6 (20.0%)	16 (26.7%)
Purpura	-	1 (3.3%)	1 (1.7%)
Rash	14 (46.7%)	19 (63.3%)	33 (55.0%)
Rash maculo-papular	1 (3.3%)	-	1 (1.7%)
Rash pruritic	-	1 (3.3%)	1 (1.7%)
Skin exfoliation	2 (6.7%)	2 (6.7%)	4 (6.7%)
Skin fissures	-	1 (3.3%)	1 (1.7%)
Skin lesion	1 (3.3%)	1 (3.3%)	2 (3.3%)
Skin maceration	-	1 (3.3%)	1 (1.7%)
Swelling face	1 (3.3%)	1 (3.3%)	2 (3.3%)
Vascular disorders	14 (46.7%)	13 (43.3%)	27 (45.0%)
Circulatory collapse	-	1 (3.3%)	1 (1.7%)
Extremity necrosis	-	1 (3.3%)	1 (1.7%)
Flushing	4 (13.3%)	3 (10.0%)	7 (11.7%)
Haematoma	1 (3.3%)	-	1 (1.7%)
Hot flush	3 (10.0%)	-	3 (5.0%)
Hypertension	5 (16.7%)	4 (13.3%)	9 (15.0%)
Hypotension	7 (23.3%)	6 (20.0%)	13 (21.7%)
Pallor	-	1 (3.3%)	1 (1.7%)
Peripheral coldness	1 (3.3%)	-	1 (1.7%)
Thrombophlebitis	-	1 (3.3%)	1 (1.7%)
Venoocclusive disease	1 (3.3%)	1 (3.3%)	2 (3.3%)

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Cardiac Toxicity

Number of events (Cardiac Toxicity AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Total number of AE	82	71	153
Cardiac disorders	50 (61.0%)	39 (54.9%)	89 (58.2%)
Atrial fibrillation	3 (3.7%)	2 (2.8%)	5 (3.3%)
Atrial flutter	1 (1.2%)	-	1 (0.7%)
Bradycardia	7 (8.5%)	8 (11.3%)	15 (9.8%)
Cardiac arrest	1 (1.2%)	-	1 (0.7%)
Cardiac failure	2 (2.4%)	-	2 (1.3%)
Cardiovascular disorder	1 (1.2%)	-	1 (0.7%)
Extrasystoles	1 (1.2%)	-	1 (0.7%)
Pericardial effusion	2 (2.4%)	-	2 (1.3%)
Sinus bradycardia	1 (1.2%)	1 (1.4%)	2 (1.3%)
Sinus tachycardia	5 (6.1%)	3 (4.2%)	8 (5.2%)
Tachyarrhythmia	1 (1.2%)	-	1 (0.7%)
Tachycardia	24 (29.3%)	25 (35.2%)	49 (32.0%)
Ventricular extrasystoles	1 (1.2%)	-	1 (0.7%)
Investigations	2 (2.4%)	1 (1.4%)	3 (2.0%)
Blood pressure diastolic decreased	1 (1.2%)	-	1 (0.7%)
Cardiac imaging procedure abnormal	1 (1.2%)	-	1 (0.7%)
Heart rate irregular	-	1 (1.4%)	1 (0.7%)
Nervous system disorders	-	7 (9.9%)	7 (4.6%)
Hypertonia	-	2 (2.8%)	2 (1.3%)
Hypotonia	-	5 (7.0%)	5 (3.3%)
Vascular disorders	30 (36.6%)	24 (33.8%)	54 (35.3%)
Hypertension	21 (25.6%)	20 (28.2%)	41 (26.8%)
Hypertensive crisis	-	1 (1.4%)	1 (0.7%)
Hypotension	9 (11.0%)	3 (4.2%)	12 (7.8%)

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

Number of patients (Cardiac Toxicity AE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Number of patients with at least one AE	26 (86.7%)	27 (90.0%)	53 (88.3%)
Cardiac disorders	19 (63.3%)	21 (70.0%)	40 (66.7%)
Atrial fibrillation	2 (6.7%)	2 (6.7%)	4 (6.7%)
Atrial flutter	1 (3.3%)	-	1 (1.7%)
Bradycardia	7 (23.3%)	7 (23.3%)	14 (23.3%)
Cardiac arrest	1 (3.3%)	-	1 (1.7%)
Cardiac failure	2 (6.7%)	-	2 (3.3%)
Cardiovascular disorder	1 (3.3%)	-	1 (1.7%)
Extrasystoles	1 (3.3%)	-	1 (1.7%)
Pericardial effusion	2 (6.7%)	-	2 (3.3%)
Sinus bradycardia	1 (3.3%)	1 (3.3%)	2 (3.3%)
Sinus tachycardia	3 (10.0%)	2 (6.7%)	5 (8.3%)
Tachyarrhythmia	1 (3.3%)	-	1 (1.7%)
Tachycardia	14 (46.7%)	17 (56.7%)	31 (51.7%)
Ventricular extrasystoles	1 (3.3%)	-	1 (1.7%)
Investigations	2 (6.7%)	1 (3.3%)	3 (5.0%)
Blood pressure diastolic decreased	1 (3.3%)	-	1 (1.7%)
Cardiac imaging procedure abnormal	1 (3.3%)	-	1 (1.7%)
Heart rate irregular	-	1 (3.3%)	1 (1.7%)
Nervous system disorders	-	3 (10.0%)	3 (5.0%)
Hypertonia	-	2 (6.7%)	2 (3.3%)
Hypotonia	-	2 (6.7%)	2 (3.3%)
Vascular disorders	19 (63.3%)	15 (50.0%)	34 (56.7%)
Hypertension	15 (50.0%)	13 (43.3%)	28 (46.7%)
Hypertensive crisis	-	1 (3.3%)	1 (1.7%)
Hypotension	8 (26.7%)	2 (6.7%)	10 (16.7%)

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Expected Leukemia

Number of events (Expected Leukemia)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Total number of AE	310	304	614
Blood and lymphatic system disorders	14 (4.5%)	13 (4.3%)	27 (4.4%)
Anaemia	14 (4.5%)	13 (4.3%)	27 (4.4%)
Eye disorders	4 (1.3%)	3 (1.0%)	7 (1.1%)
Conjunctival haemorrhage	2 (0.6%)	-	2 (0.3%)
Eye haemorrhage	2 (0.6%)	3 (1.0%)	5 (0.8%)
Gastrointestinal disorders	137 (44.2%)	140 (46.1%)	277 (45.1%)
Anal haemorrhage	1 (0.3%)	1 (0.3%)	2 (0.3%)
Intestinal haemorrhage	-	1 (0.3%)	1 (0.2%)
Mouth haemorrhage	2 (0.6%)	7 (2.3%)	9 (1.5%)
Nausea	65 (21.0%)	62 (20.4%)	127 (20.7%)
Rectal haemorrhage	-	1 (0.3%)	1 (0.2%)
Stomatitis	16 (5.2%)	10 (3.3%)	26 (4.2%)
Vomiting	53 (17.1%)	58 (19.1%)	111 (18.1%)
General disorders and administration site conditio	87 (28.1%)	71 (23.4%)	158 (25.7%)
Catheter site haemorrhage	1 (0.3%)	2 (0.7%)	3 (0.5%)
Mucosal haemorrhage	-	1 (0.3%)	1 (0.2%)
Mucosal inflammation	17 (5.5%)	14 (4.6%)	31 (5.0%)
Pyrexia	69 (22.3%)	54 (17.8%)	123 (20.0%)
Infections and infestations	1 (0.3%)	1 (0.3%)	2 (0.3%)
Herpes simplex	1 (0.3%)	-	1 (0.2%)
Oral herpes	-	1 (0.3%)	1 (0.2%)
Investigations	30 (9.7%)	43 (14.1%)	73 (11.9%)
Lymphocyte count decreased	2 (0.6%)	10 (3.3%)	12 (2.0%)
Neutrophil count decreased	7 (2.3%)	16 (5.3%)	23 (3.7%)
Platelet count decreased	13 (4.2%)	12 (3.9%)	25 (4.1%)
White blood cell count decreased	8 (2.6%)	5 (1.6%)	13 (2.1%)
Nervous system disorders	-	1 (0.3%)	1 (0.2%)
Cerebral haemorrhage	-	1 (0.3%)	1 (0.2%)
Renal and urinary disorders	2 (0.6%)	2 (0.7%)	4 (0.7%)
Haematuria	2 (0.6%)	2 (0.7%)	4 (0.7%)
Reproductive system and breast disorders	2 (0.6%)	3 (1.0%)	5 (0.8%)
Menstrual disorder	1 (0.3%)	2 (0.7%)	3 (0.5%)
Vaginal haemorrhage	1 (0.3%)	1 (0.3%)	2 (0.3%)
Respiratory, thoracic and mediastinal disorders	11 (3.5%)	16 (5.3%)	27 (4.4%)
Bronchial haemorrhage	1 (0.3%)	-	1 (0.2%)
Epistaxis	10 (3.2%)	14 (4.6%)	24 (3.9%)

Number of events (Expected Leukemia)

	Treatment arm - CODELIST		
System Organ Class Preferred Term	**ClAraC N=30**	**FLAMSA N=30**	**Total N=60**
Haemoptysis	-	2 (0.7%)	2 (0.3%)
Skin and subcutaneous tissue disorders	14 (4.5%)	4 (1.3%)	18 (2.9%)
Petechiae	13 (4.2%)	4 (1.3%)	17 (2.8%)
Purpura	1 (0.3%)	-	1 (0.2%)
Vascular disorders	8 (2.6%)	7 (2.3%)	15 (2.4%)
Arterial haemorrhage	-	1 (0.3%)	1 (0.2%)
Capillary leak syndrome	2 (0.6%)	1 (0.3%)	3 (0.5%)
Haematoma	1 (0.3%)	4 (1.3%)	5 (0.8%)
Haemorrhage	5 (1.6%)	1 (0.3%)	6 (1.0%)

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.

Number of patients (Expected Leukemia)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Number of patients with at least one AE	30 (100.0%)	30 (100.0%)	60 (100.0%)
Blood and lymphatic system disorders	6 (20.0%)	6 (20.0%)	12 (20.0%)
Anaemia	6 (20.0%)	6 (20.0%)	12 (20.0%)
Eye disorders	4 (13.3%)	3 (10.0%)	7 (11.7%)
Conjunctival haemorrhage	2 (6.7%)	-	2 (3.3%)
Eye haemorrhage	2 (6.7%)	3 (10.0%)	5 (8.3%)
Gastrointestinal disorders	30 (100.0%)	30 (100.0%)	60 (100.0%)
Anal haemorrhage	1 (3.3%)	1 (3.3%)	2 (3.3%)
Intestinal haemorrhage	-	1 (3.3%)	1 (1.7%)
Mouth haemorrhage	2 (6.7%)	4 (13.3%)	6 (10.0%)
Nausea	29 (96.7%)	27 (90.0%)	56 (93.3%)
Rectal haemorrhage	-	1 (3.3%)	1 (1.7%)
Stomatitis	10 (33.3%)	8 (26.7%)	18 (30.0%)
Vomiting	22 (73.3%)	25 (83.3%)	47 (78.3%)
General disorders and administration site conditio	28 (93.3%)	28 (93.3%)	56 (93.3%)
Catheter site haemorrhage	1 (3.3%)	1 (3.3%)	2 (3.3%)
Mucosal haemorrhage	-	1 (3.3%)	1 (1.7%)
Mucosal inflammation	12 (40.0%)	13 (43.3%)	25 (41.7%)
Pyrexia	28 (93.3%)	27 (90.0%)	55 (91.7%)
Infections and infestations	1 (3.3%)	1 (3.3%)	2 (3.3%)
Herpes simplex	1 (3.3%)	-	1 (1.7%)
Oral herpes	-	1 (3.3%)	1 (1.7%)
Investigations	7 (23.3%)	6 (20.0%)	13 (21.7%)
Lymphocyte count decreased	1 (3.3%)	4 (13.3%)	5 (8.3%)
Neutrophil count decreased	3 (10.0%)	6 (20.0%)	9 (15.0%)
Platelet count decreased	7 (23.3%)	6 (20.0%)	13 (21.7%)
White blood cell count decreased	6 (20.0%)	5 (16.7%)	11 (18.3%)
Nervous system disorders	-	1 (3.3%)	1 (1.7%)
Cerebral haemorrhage	-	1 (3.3%)	1 (1.7%)
Renal and urinary disorders	2 (6.7%)	2 (6.7%)	4 (6.7%)
Haematuria	2 (6.7%)	2 (6.7%)	4 (6.7%)
Reproductive system and breast disorders	2 (6.7%)	2 (6.7%)	4 (6.7%)
Menstrual disorder	1 (3.3%)	2 (6.7%)	3 (5.0%)
Vaginal haemorrhage	1 (3.3%)	1 (3.3%)	2 (3.3%)
Respiratory, thoracic and mediastinal disorders	7 (23.3%)	10 (33.3%)	17 (28.3%)
Bronchial haemorrhage	1 (3.3%)	-	1 (1.7%)
Epistaxis	6 (20.0%)	10 (33.3%)	16 (26.7%)

Number of patients (Expected Leukemia)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Haemoptysis	-	1 (3.3%)	1 (1.7%)
Skin and subcutaneous tissue disorders	10 (33.3%)	4 (13.3%)	14 (23.3%)
Petechiae	9 (30.0%)	4 (13.3%)	13 (21.7%)
Purpura	1 (3.3%)	-	1 (1.7%)
Vascular disorders	7 (23.3%)	6 (20.0%)	13 (21.7%)
Arterial haemorrhage	-	1 (3.3%)	1 (1.7%)
Capillary leak syndrome	2 (6.7%)	1 (3.3%)	3 (5.0%)
Haematoma	1 (3.3%)	4 (13.3%)	5 (8.3%)
Haemorrhage	5 (16.7%)	1 (3.3%)	6 (10.0%)

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Serious Adverse Events

Number of events (SAE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Total number of SAE	20	18	38
Cardiac disorders	3 (15.0%)	-	3 (7.9%)
Atrial fibrillation	1 (5.0%)	-	1 (2.6%)
Atrial flutter	1 (5.0%)	-	1 (2.6%)
Cardiac arrest	1 (5.0%)	-	1 (2.6%)
Gastrointestinal disorders	-	1 (5.6%)	1 (2.6%)
Oesophagitis	-	1 (5.6%)	1 (2.6%)
General disorders and administration site conditio	3 (15.0%)	-	3 (7.9%)
Disease progression	1 (5.0%)	-	1 (2.6%)
Multiple organ dysfunction syndrome	1 (5.0%)	-	1 (2.6%)
Pyrexia	1 (5.0%)	-	1 (2.6%)
Hepatobiliary disorders	1 (5.0%)	-	1 (2.6%)
Hepatic failure	1 (5.0%)	-	1 (2.6%)
Infections and infestations	3 (15.0%)	7 (38.9%)	10 (26.3%)
Cytomegalovirus infection	1 (5.0%)	-	1 (2.6%)
Enterococcal infection	-	1 (5.6%)	1 (2.6%)
Intestinal sepsis	-	1 (5.6%)	1 (2.6%)
Pneumonia	-	1 (5.6%)	1 (2.6%)
Sepsis	2 (10.0%)	2 (11.1%)	4 (10.5%)
Septic shock	-	1 (5.6%)	1 (2.6%)
Viral haemorrhagic cystitis	-	1 (5.6%)	1 (2.6%)
Injury, poisoning and procedural complications	-	1 (5.6%)	1 (2.6%)
Transplant failure	-	1 (5.6%)	1 (2.6%)
Investigations	1 (5.0%)	-	1 (2.6%)
Blood lactic acid increased	1 (5.0%)	-	1 (2.6%)
Metabolism and nutrition disorders	2 (10.0%)	1 (5.6%)	3 (7.9%)
Acidosis	-	1 (5.6%)	1 (2.6%)
Hypervolaemia	1 (5.0%)	-	1 (2.6%)
Tumour lysis syndrome	1 (5.0%)	-	1 (2.6%)
Neoplasms benign, malignant and unspecified (incl	2 (10.0%)	-	2 (5.3%)
Acute myeloid leukaemia	2 (10.0%)	-	2 (5.3%)
Nervous system disorders	-	2 (11.1%)	2 (5.3%)
Cerebral haemorrhage	-	1 (5.6%)	1 (2.6%)
Coma	-	1 (5.6%)	1 (2.6%)
Renal and urinary disorders	1 (5.0%)	3 (16.7%)	4 (10.5%)

Number of events (SAE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Acute kidney injury	1 (5.0%)	2 (11.1%)	3 (7.9%)
Renal failure	-	1 (5.6%)	1 (2.6%)
Respiratory, thoracic and mediastinal disorders	1 (5.0%)	2 (11.1%)	3 (7.9%)
Hypoxia	1 (5.0%)	-	1 (2.6%)
Respiratory failure	-	2 (11.1%)	2 (5.3%)
Vascular disorders	3 (15.0%)	1 (5.6%)	4 (10.5%)
Capillary leak syndrome	2 (10.0%)	-	2 (5.3%)
Hypotension	1 (5.0%)	-	1 (2.6%)
Venoocclusive disease	-	1 (5.6%)	1 (2.6%)

Table includes all SAEs. Percentages are calculated using the total number of events per treatment group as the denominator.

Number of patients (SAE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Number of patients with at least one SAE	7 (23.3%)	7 (23.3%)	14 (23.3%)
Cardiac disorders	2 (6.7%)	-	2 (3.3%)
Atrial fibrillation	1 (3.3%)	-	1 (1.7%)
Atrial flutter	1 (3.3%)	-	1 (1.7%)
Cardiac arrest	1 (3.3%)	-	1 (1.7%)
Gastrointestinal disorders	-	1 (3.3%)	1 (1.7%)
Oesophagitis	-	1 (3.3%)	1 (1.7%)
General disorders and administration site conditio	3 (10.0%)	-	3 (5.0%)
Disease progression	1 (3.3%)	-	1 (1.7%)
Multiple organ dysfunction syndrome	1 (3.3%)	-	1 (1.7%)
Pyrexia	1 (3.3%)	-	1 (1.7%)
Hepatobiliary disorders	1 (3.3%)	-	1 (1.7%)
Hepatic failure	1 (3.3%)	-	1 (1.7%)
Infections and infestations	3 (10.0%)	5 (16.7%)	8 (13.3%)
Cytomegalovirus infection	1 (3.3%)	-	1 (1.7%)
Enterococcal infection	-	1 (3.3%)	1 (1.7%)
Intestinal sepsis	-	1 (3.3%)	1 (1.7%)
Pneumonia	-	1 (3.3%)	1 (1.7%)
Sepsis	2 (6.7%)	2 (6.7%)	4 (6.7%)
Septic shock	-	1 (3.3%)	1 (1.7%)
Viral haemorrhagic cystitis	-	1 (3.3%)	1 (1.7%)
Injury, poisoning and procedural complications	-	1 (3.3%)	1 (1.7%)
Transplant failure	-	1 (3.3%)	1 (1.7%)
Investigations	1 (3.3%)	-	1 (1.7%)
Blood lactic acid increased	1 (3.3%)	-	1 (1.7%)
Metabolism and nutrition disorders	2 (6.7%)	1 (3.3%)	3 (5.0%)
Acidosis	-	1 (3.3%)	1 (1.7%)
Hypervolaemia	1 (3.3%)	-	1 (1.7%)
Tumour lysis syndrome	1 (3.3%)	-	1 (1.7%)
Neoplasms benign, malignant and unspecified (incl	2 (6.7%)	-	2 (3.3%)
Acute myeloid leukaemia	2 (6.7%)	-	2 (3.3%)
Nervous system disorders	-	2 (6.7%)	2 (3.3%)
Cerebral haemorrhage	-	1 (3.3%)	1 (1.7%)
Coma	-	1 (3.3%)	1 (1.7%)
Renal and urinary disorders	1 (3.3%)	3 (10.0%)	4 (6.7%)
Acute kidney injury	1 (3.3%)	2 (6.7%)	3 (5.0%)

Number of patients (SAE)

System Organ Class Preferred Term	Treatment arm - CODELIST ClAraC N=30	 FLAMSA N=30	 Total N=60
Renal failure	-	1 (3.3%)	1 (1.7%)
Respiratory, thoracic and mediastinal disorders	1 (3.3%)	2 (6.7%)	3 (5.0%)
Hypoxia	1 (3.3%)	-	1 (1.7%)
Respiratory failure	-	2 (6.7%)	2 (3.3%)
Vascular disorders	2 (6.7%)	1 (3.3%)	3 (5.0%)
Capillary leak syndrome	2 (6.7%)	-	2 (3.3%)
Hypotension	1 (3.3%)	-	1 (1.7%)
Venoocclusive disease	-	1 (3.3%)	1 (1.7%)

Table includes each SAE term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.