CLINICAL STUDY REPORT - SCIENTIFIC SUMMARY

Study Title:	Multicenter, semi-blinded, randomized, controlled, parallel arms clinical study on the performance of SGM-101, a fluorochrome-labeled anti-carcino-embryonic antigen (CEA) monoclonal antibody, for the delineation of primary and recurrent tumor and metastases in patients undergoing curative surgery for colorectal cancer.
Short Study Title:	SGM-101 performance in patients undergoing surgery for colorectal cancer.
Study Number:	SGM-CLIN03
Regulatory Agency:	IND number: 134725 EudraCT number: 2018-000151-40
Sponsor:	SurgiMab 10, Parc Club du Millénaire 1025, avenue Henri Becquerel 34000 Montpellier, France
Sponsor's Responsible Medical Officer:	Françoise Cailler, Chief Scientific Officer
Contract Research Organization:	iLIFE Consulting 115, rue Lafayette 75010 Paris, France
Study Phase:	Phase 3
Test Product:	SGM-101
Indication:	Patients undergoing surgery for colorectal cancer with a curative intent
Study Initiation Date (First Patient Enrolled):	22 May 2019
Study Completion Date:	12 Feb 2025
Report Version and Date:	Clinical Study Report, version 2.0, 12 Feb 2026

This study was conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

This Scientific Synopsis summarizes the Key elements and results of the Phase 3 study SGM-CLIN03.The complete Study Report is available to regulatory authorities upon request.

1. Clinical study presentation

Name of Sponsor/Company and Scientific and Public Contact Points: SurgiMab

Scientific and Public Contact Point: Françoise Cailler, CSO

Name of Finished Investigational Product (IP): SGM-101

Name of Active Ingredient: Carcino-embryonic antigen (CEA)-specific chimeric antibody conjugated with a near-infrared (NIR) emitting fluorochrome developed as an intraoperative imaging agent for the delineation and/or detection of malignant tissue.

Indication: Patients undergoing surgery for colorectal cancer with a curative intent.

Study Number: SGM-CLIN03

Regulatory Agency Identifier Numbers:
- IND number: 134725
- EudraCT number: 2018-000151-40

Pediatric Investigation Plan and/or Pediatric Study Plan Number: Not applicable

Study Title: Multicenter, semi-blinded, randomized, controlled, parallel arms clinical study on the performance of SGM-101, a fluorochrome-labeled anti-carcino-embryonic antigen (CEA) monoclonal antibody, for the delineation of primary and recurrent tumor and metastases in patients undergoing curative surgery for colorectal cancer.

Short Study Title: SGM-101 performance in patients undergoing surgery for colorectal cancer.

Study Phase: Phase 3

Number of Study Sites and Countries: The study enrolled patients from 12 investigative sites in the United States (US) and Europe.

Principal/Coordinating Investigator Name: Alexander L. Vahrmeijer, MD, PhD

Publication (References): None

Study Period:
- Date of First Patient: 22 May 2019
- Date of Last Patient Completed: 12 Feb 2025

2. Background and Rationale for the Study:

SurgiMab is developing antibody-fluorochrome conjugates as in vivo intraoperative imaging agents in oncology. SGM-101 is a fluorescent conjugate comprised of a tumor-specific, anti-CEA monoclonal antibody and a NIR emitting fluorochrome. CEA is overexpressed in a wide range of human carcinomas, including colorectal, gastric, pancreatic, non-small cell lung, and breast carcinomas.

Technological advances have been made in cancer diagnostics and therapeutics during the last years to compensate for the high rate of death due to cancer over the world. Although modern surgical advancements have improved surgical oncology, adequate tumor visualization remains a limitation preventing total removal of cancer tissue. Surgeons rely primarily on white light (WL) reflectance, which limits the differentiation between healthy tissue and tumor and can lead to residual cancer cells inadvertently left behind. Oncologic surgeons agree that advances in fluorescence imaging using targeted probes to enhance the visual capability of the operating surgeon beyond that of WL reflectance would provide a major opportunity to improve outcomes. The goal of administration of SGM-101 was to provide oncologic surgeons with an intraoperative imaging tool that could offer them pseudo-color distinction between tumor and adjacent normal tissue thus allowing them to visualize and delineate tumors overexpressing CEA, particularly colorectal tumors and their metastases.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary Objective	Primary Endpoint
To analyze the clinical benefit resulting from the use of FGS during the surgical procedure, with SGM-101 as the intraoperative imaging agent, in terms of additional cancer lesions detected with the goal to achieving R0 resection.	**Detection rate: E1**, defined as the proportion of patients in whom NIR allowed to: 1. achieve tumor free surgical margins of lesions identified before the use of NIR, when WL alone did not (R0 resection) AND/OR 2. identify and resect at least one additional TP, i.e., only [WL negative, NIR positive, pathology positive] tumor lesion (core lesion and/or margins and/or re-resection) in patients in which WL allowed to achieve tumor free margins (R0) for all lesions identified before the use of NIR OR 3. identify and resect at least one additional TP tumor lesion (core lesion and/or margins and/or re-resection) in patients undergoing a debulking surgery before a HIPEC procedure [HIPEC subgroup] The 3 individual components of E1 (E1.1, E1.2 and E1.3) were also analyzed separately.

Summary of the Attributes of the Estimand for the Primary Endpoint – Main Analysis

Target population: all patients randomized to SGM-101, having received the SGM-101 injection and having undergone surgery for colorectal cancer with fluorescence assessment

Treatment: SGM-101 injection, whatever the dose administered, followed by surgical treatment first with conventional tumor assessment followed with fluorescence tumor assessment.

Endpoint: detection rate E1

Population-level summary: percentage of patients meeting endpoint E1 over the total number of patients in the target population

Intercurrent events and strategies to handle those:

- ICE1, ICE3, ICE4, ICE5: patients were excluded from the population (Principal Stratum strategy);
- ICE2: patients were considered irrelevant in defining the treatment effect of interest (Treatment policy estimand).

Events leading to missing data and strategies to handle those:

- Patients with a missing endpoint E1 were imputed as negative if none of its 3 components (E1.1, E1.2, and E1.3) could be assessed. If any of the 3 components was assessed as positive, the primary endpoint was positive, if all available components were negative, the primary endpoint was considered as negative.

Key Secondary Efficacy Objective	Key Secondary Efficacy Endpoint
To analyze the clinical benefit resulting from the use of FGS during the surgical procedure, with SGM-101 as the intraoperative imaging agent, in terms of preservation of non-cancer tissue.	**Conservative surgery benefit rate: E2**, defined as the proportion of patients who had more [WL positive, NIR negative, pathology negative] (NIR TN) lesions than [WL negative, NIR positive, pathology negative] (NIR FP) lesions, i.e., a net benefit in numbers of negative lesions wrongly resected.

Summary of the Attributes of the Estimand for the Key Secondary Efficacy Endpoint – Main Analysis

Target population: all patients randomized to SGM-101, having received the SGM-101 injection and having undergone surgery for colorectal cancer with fluorescence assessment

Treatment: SGM-101 injection, whatever the dose administered, followed by surgical treatment first with conventional tumor assessment followed with fluorescence tumor assessment.

Endpoint: conservative surgery benefit rate E2

Population-level summary: percentage of patients meeting endpoint E2 over the total number of patients in the target population with at least one negative histopathology result that can be compared to the NIR and WL visualization

Intercurrent events and strategies to handle those:

- ICE1, ICE3, ICE4, ICE5: patients were excluded from the population (Principal Stratum strategy);

- ICE2: patients were considered irrelevant in defining the treatment effect of interest (Treatment policy estimand).

Events leading to missing data and strategies to handle those:

- Patients with a missing endpoint E2 were imputed as absence of conservative surgery benefit.

Other Secondary Efficacy Objectives	Other Secondary Efficacy Endpoints
To analyze the false detection rate of FGS during the surgical procedure, with SGM-101 as the intraoperative imaging agent.	**False detection rate: E3**, defined as the proportion of patients who had all additional biopsies/resections under NIR that were FP, i.e., only [WL negative, NIR positive, pathology negative] and no [WL negative, NIR positive, pathology positive].

Summary of the Attributes of the Estimand for the Other Secondary Efficacy Endpoint E3 – Main Analysis

Target population: all patients randomized to SGM-101, having received the SGM-101 injection and having undergone surgery for colorectal cancer with fluorescence assessment

Treatment: SGM-101 injection, whatever the dose administered, followed by surgical treatment first with conventional tumor assessment followed with fluorescence tumor assessment.

Endpoint: false detection rate E3

Population-level summary: percentage of patients meeting endpoint E3 over the total number of patients in the target population with at least one additional biopsy/resection due to NIR

Intercurrent events and strategies to handle those:

- ICE1, ICE3, ICE4, ICE5: patients were excluded from the population (Principal Stratum strategy)
- ICE2: patients were considered irrelevant in defining the treatment effect of interest (Treatment policy estimand)

Events leading to missing data and strategies to handle those:

- Patients with a missing endpoint E3 were imputed as presence of false detection.

Other Secondary Efficacy Objectives	Other Secondary Efficacy Endpoints
To analyze the clinical benefit resulting from the use of FGS during the surgical procedure, with SGM-101 as the intraoperative imaging agent, in terms of overall benefit.	**Clinical benefit rate (any "positive" change in the surgical plan or post-surgical management of the patient resulting from the use of FGS): E4**, was a composite endpoint assessed at the patient level patient by comparing standard of care surgery without fluorescence to surgery with fluorescence and assessing if the latter allowed: • to remove any additional pathologically confirmed malignant lesion

	AND/OR • to resect less (pathologically confirmed) non-malignant tissue AND/OR • to adapt the post-surgical management in case of detection with NIR only of unsuspected new lesions, leading to a re-staging of the disease. This was the definition of endpoint E4 from former versions of the protocol. As no information on the post chirurgical management of the patient was captured in the eCRF, this component of the endpoint could not be evaluated and was discarded. The impact, if any, was an underestimation of the E4 rate. each patient serving as his own control. The outcome measure was the rate of patients with clinical benefit.

Summary of the Attributes of the Estimand for the Other Secondary Efficacy Endpoint E4 – Main Analysis

Target population: all patients randomized to SGM-101, having received the SGM-101 injection and having undergone surgery for colorectal cancer with fluorescence assessment

Treatment: SGM-101 injection, whatever the dose administered, followed by surgical treatment first with conventional tumor assessment followed with fluorescence tumor assessment.

Endpoint: clinical benefit rate E4

Population-level summary: percentage of patients meeting endpoint E4 over the total number of patients in the target population

Intercurrent events and strategies to handle those:

- ICE1, ICE3, ICE4, ICE5: patients were excluded from the population (Principal Stratum strategy);
- ICE2: patients were considered irrelevant in defining the treatment effect of interest (Treatment policy estimand).

Events leading to missing data and strategies to handle those:

- Patients with a missing endpoint E4 were imputed as absence of clinical benefit.

Other Secondary Efficacy Objectives	Other Secondary Efficacy Endpoints
To analyze the benefit (observed or potential) resulting from the expected better performance of FGS during the surgical procedure, with SGM-101 as the intraoperative imaging agent, compared to WL alone.	**Rate of FGS benefit over WL alone: E5**, was a composite endpoint assessed at the patient level. At the individual zone of interest level, all FGS vs. WL discordant results were reviewed to evaluate which of FGS or WL agreed with pathology results. If FGS was consistent with pathology the

	FGS had a positive outcome. When FGS was discordant with pathology then it had or would have had a negative outcome. All concordant FGS and WL results were considered as neutral (neither benefit nor harm from FGS over WL). Lesions with FGS and WL concordant results received a neutral assessment. At the patient level, if the number of individual resection positive results was greater than the number of individual resection negative results, the overall result was considered as positive. It was considered as negative in all other cases (greater number of individual resections negative outcome, equal numbers of negative and positive individual resections outcomes, or only neutral individual resection outcomes).

Summary of the Attributes of the Estimand for the Other Secondary Efficacy Endpoint E5 – Main Analysis

Target population: all patients randomized to SGM-101, having received the SGM-101 injection and having undergone surgery for colorectal cancer with fluorescence assessment

Treatment: SGM-101 injection, whatever the dose administered, followed by surgical treatment first with conventional tumor assessment followed with fluorescence tumor assessment.

Endpoint: rate of FGS benefit over WL alone E5

Population-level summary: percentage of patients meeting endpoint E5 over the total number of patients in the target population

Intercurrent events and strategies to handle those:

- ICE1, ICE3, ICE4, ICE5: patients were excluded from the population (Principal Stratum strategy);
- ICE2: patients were considered irrelevant in defining the treatment effect of interest (Treatment policy estimand).

Events leading to missing data and strategies to handle those:

- Patients with a missing endpoint E5 were imputed as absence of FGS benefit over WL alone.

Other Secondary Efficacy Objectives	Other Secondary Efficacy Endpoints
Diagnostic performance of FGS: Se To analyze the diagnostic sensitivity of FGS with SGM-101 as intraoperative imaging agent by reference to the pathology results (final pathology when available or FFS if not sent to pathology) with respect to the presence of cancer, for all lesions including	**Sensitivity rate: E6**, was used as the main endpoint to assess the performance of the intraoperative imaging agent. The sensitivity ratio (malignant results correctly identified by fluorescence) was computed as the ratio of TP over the sum of TP + FN (i.e., all histopathological malignant lesions):

additional lesions identified with fluorescent light only.	Se=TP/(TP+FN) It was computed at the zone of interest level.
Diagnostic performance of FGS: FPR To analyze the diagnostic FPR of FGS with SGM-101 as intraoperative imaging agent by reference to the pathology results (final pathology when available or FFS if not sent to pathology) with respect to the presence of cancer, for all lesions including additional lesions identified with fluorescent light only.	**FPR E7** (non-malignant lesions wrongly identified by fluorescence as malignant) was equal to 1-the PPV. It was computed as the ratio of FP over the sum of TP + FP: FPR = (1-PPV) = FP/(TP+FP) It was computed at the zone of interest level.
To further characterize diagnostic performance by analyzing the PPV, NPV, Sp, and accuracy of FGS using SGM-101 as intraoperative imaging agent in identifying positive (malignant) tumor lesions and/or positive resection margins by comparison with the histopathology results (final pathology when available or FFS if not sent to pathology), the current gold standard, for 1) all lesions and 2) additional lesions identified with fluorescent light only.	**PPV** (percentage of histologically positive lesions among fluorescent lesions), **NPV** (percentage of histologically negative lesions among non-fluorescent lesions), **Sp ratio** (non-malignant results correctly identified by fluorescence), and **Accuracy rate** (percentage of accurate identification by NIR [TP and TN] as confirmed histologically) were computed at the zone of interest level.

<u>Summary of the Attributes of the Estimand for the Other Secondary Efficacy Endpoints assessing Diagnostic Performance (E6, E7, PPV, NPV, Sp, and Accuracy) – Main Analysis</u>

Target population: all patients randomized to SGM-101, having received the SGM-101 injection, having undergone surgery for colorectal cancer, having at least some tissue ablated and evaluated in NIR or information on FGS performance in case of no ablation.

Treatment: SGM-101 injection, whatever the dose administered, followed by surgical treatment first with conventional tumor assessment followed with fluorescence tumor assessment.

Endpoint: rate of E6, E7, PPV, NPV, Sp, or accuracy

Population-level summary: rate of E6, E7, PPV, NPV, Sp, or accuracy expressed as ratio

Intercurrent events and strategies to handle those:

- ICE1, ICE3, ICE4, ICE5: patients were excluded from the population (Principal Stratum strategy);
- ICE2: patients were considered irrelevant in defining the treatment effect of interest (Treatment policy estimand).

Events leading to missing data and strategies to handle those:

- For patients with missing central histopathological results, the local histopathological results if available, and the FFS results if neither central nor local results were available, were used.

Other Secondary Efficacy Objectives	Other Secondary Efficacy Endpoints
Diagnostic performance of FGS vs. FFS	The diagnostic performance of FGS was analyzed on the subgroup of patients with FFS taken during surgery, to assess if FGS could replace FFS, resulting in a potential benefit on the total duration of the surgical procedure.
To describe the TBR	TBR, defined as fluorescent signal of tumor tissue compared to fluorescence signal of normal tissue surrounding the tumor
To document the impact of SGM-101 injection on the surgical procedure	The impact of SGM-101 injection on the surgical procedure (rapidity of the evaluation, easiness of detection of additional nodules, duration of surgical procedure, duration of anesthesia) was assessed using a surgeon's questionnaire.

Secondary Safety Objectives	Secondary Safety Endpoints
To evaluate tolerability/safety of SGM-101 injection	Routine clinical measurements such as TEAEs, vital signs, ECG, physical findings, and routine laboratory assessments
To evaluate short-term surgical outcomes	Assessment of AEs related to surgery within a period of 32 days following SGM-101 injection in order to substantiate the benefit/risk assessment of the use of SGM-101 and assess a possible bias in the surgeons' approach due to the use of fluorescence

Exploratory Objectives	Exploratory Endpoints
To assess the PK, safety and tolerability of a single intravenous injection of 10 mg of SGM-101	The PK analysis consisted in computing the C_{max}, T½, AUC, T_{max}, and clearance at Day -4, Day 0, and Day 5
To assess the immunogenicity of SGM-101 by dosage of ADA	Immunogenicity of SGM-101 was assessed by dosage of ADA at Day -4, Day 5, and at Day 28

ADA=anti-drug antibody; AE=adverse event; AUC=area under the concentration vs. time curve; Cmax=maximum concentration; D=day; eCRF=electronic case report form; FFS=fresh frozen section; FGS=fluorescence-guided surgery; FN=false negative; FP=false positive; FPR=false positive rate; HIPEC=hyperthermic intraperitoneal chemotherapy; ICE=intercurrent event; NIR=near-infrared; NPV=negative predictive value; PK=pharmacokinetic(s); PPV=positive predictive value; Se=sensitivity; Sp=specificity; T1/2=terminal half-life; TBR=tumor-to-background ratio; TEAE=treatment-emergent adverse event; Tmax=time to maximum concentration; TN=true negative; TP=true positive; WL=white light

Note: ICEs were defined as follows:

- ICE1: absence of treatment with SGM-101 in a patient randomized to the SGM-101 arm
- ICE2: non-compliance with study treatment (dose or delay prior to surgery)
- ICE3: absence of surgery in a patient randomized to SGM-101 and treated as planned
- ICE4: absence of ablation of any tissue together with absence of any information allowing to assess the performance of FGS: the patient underwent the surgical procedure, but no ablation of any tissue was performed resulting in the absence of any histopathological result (neither from resected tissue nor from FFS) because of the surgeon decision based on his evaluation during the procedure, and no information was available about the contribution of FGS to this decision
- ICE5: NIR camera failure preventing the FGS assessment

4. Methodology:

This was a randomized, controlled, semi-blinded, parallel-arm, multicenter, Phase 3 study on the performance of SGM-101, a fluorochrome-labeled anti-CEA monoclonal antibody, for the delineation of primary tumor, recurrent disease, and metastases in patients undergoing curative surgery for colorectal cancer.

The main objective of this study was to assess the performance of SGM-101 in the intraoperative detection of resection margins and metastases in patients undergoing curative surgery for colorectal cancer. The control was standard operating conditions without fluorescence assessment, that is designed as WL surgery. Each patient in the SGM-101 arm was his own control.

Patients were randomized with an unbalanced randomization ratio of 4:1 (SGM-101 guided surgery: saline injection and standard surgical treatment). The randomization was stratified according to 2 stratification factors (tumor location/type and geographical regions). The control arm (saline injection, followed by standard surgical treatment) allows to assess the influence of SGM-101-induced fluorescence upon the safety of the surgical intervention.

The study was conducted using a semi-blinded design. The initial surgical assessment was performed under blinded conditions without access to fluorescence imaging, followed by unblinding, and use of fluorescence-guided surgery according to randomization. Patients remained blinded to treatment allocation until the end-of-study visit to minimize potential biases in safety assessment.

For each patient the study period was approximately 5 weeks. One to 6 weeks before the administration of SGM-101, eligibility of the patient was assessed. Four days before surgery, the patient was admitted to the hospital for 8 hours for SGM-101 or saline administration and assessments. Each patient was administered a single dose of either SGM-101 or saline, according to randomization. Following routine care, the patient was admitted for surgery and other protocol-related assessments. The duration of admission was based on the clinical post-operative course of the individual patient. Follow-up visits were planned on the day of discharge and Day 28 (±3 days).

An interim analysis was to be conducted after 180 patients had been randomized and had reached the Day 28 follow-up visit. This interim analysis aimed at stopping the study for futility, in case the observed results suggested that the probability of demonstrating a detection rate of SGM-101 greater than 5% with the planned sample size of 240 patients in the SGM-101 arm was too low.

An independent Data Monitoring Committee (DMC) was constituted and continuously monitored the safety profile and study progress to ensure that the study was conducted with the highest safety, scientific, and ethical standards. In addition, the DMC reviewed the planned futility analysis.

5. Number of Patients (Planned and Analyzed):

It was anticipated that 300 patients (240 in the SGM-101 arm and 60 in the saline arm) at approximately 10 international investigative sites would be enrolled. The actual number of patients enrolled was 242 at 12 investigative sites in the US and in Europe (67 patients in the US, 131 patients in the Netherlands, 27 patients in Germany, and 17 patients in Italy).

6. Diagnosis and Main Criteria for Inclusion and Exclusion:

The following inclusion criteria had to be met for a patient to be eligible for inclusion in the study:

1. Patients aged over 18 years old.
2. Patients should be scheduled for curative colorectal cancer surgery of primary cT4 colon cancer or primary clinical stage T3/4 (cT3/4) rectal cancer, recurrent colorectal cancer, or peritoneal metastasized colorectal cancer.
3. Female patients should not be of childbearing potential (i.e., women with functioning ovaries who had a documented tubal ligation or hysterectomy, ovariectomy or women who were post-menopausal) nor breastfeeding. Women of childbearing potential, including women with a documented tubal ligation, were included provided that they had a negative highly sensitive urine pregnancy test or a negative serum pregnancy test at the day of the injection and agree to practice adequate contraception for 30 days prior to administration of IP, and 90 days after completion of injection. A post-menopausal state was defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range could be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement was insufficient.
4. Patients should be capable and willing to give informed consent before study-specific procedures.

A patient who met any of the following exclusion criteria was not eligible for inclusion in the study:

1. Other malignancies either currently active or diagnosed in the last 5 years, except for adequately treated in situ carcinoma of the cervix and basal or squamous cell skin carcinoma.
2. Primary appendiceal cancer.

3. Laboratory abnormalities defined as:

   • Aspartate aminotransferase, alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), or alkaline phosphatase (ALP) levels above 5 times the upper limit of normal (ULN) or;
   • Total bilirubin above 2 times the ULN or;
   • Serum creatinine above 1.5 times the ULN or;
   • Platelet count below 100 x 109/L or;
   • Hemoglobin below 4 mmol/L (females) or below 5 mmol/L (males).

4. Known positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody or patients with untreated serious infections.
5. Use of another investigational drug within 4 weeks before the injection day.
6. Any condition that the investigator considered it could potentially jeopardize the patient's well-being or the study objectives, such as severe anaphylactic reaction in medical history, previous allergic reaction to SGM-101 or to any excipient present in the product or known hypersensitivity to murine proteins

7. Test Product, Dose, Mode of Administration, and Batch Number(s)

Patients in the SGM-101 arm received SGM-101 at the dose of 10 mg, administered as single intravenous injection over 30 minutes. The imaging system used during surgery was either the "Spectrum Platform" from Quest Medical Imaging or the "RED System" from Karl Storz.

Batch numbers: SGM1010618-A; SGM1011020-A.

8. Control Product, Dose, Mode of Administration, and Batch Number(s)

Patients in the saline arm received 100 mL saline administered as single intravenous injection over 30 minutes. The imaging system used during surgery was either the "Spectrum Platform" from Quest Medical Imaging or the "RED System" from Karl Storz.

Batch numbers:

• US: Fresenius 100 mL NaCl bags, ref FUE1335: batches 12MHE07 (exp 08/2020), 12NAE04 (exp 01/2021), 12PFE03 (exp 06/2022), 12PLE05 (exp 11/2022), 12SEE07 (exp 05/2024) and 12TEE08 (exp 04/2025);
• Europe: Fresenius 100 mL NaCl bags, ref B2448951: batches 13MKS021 (exp 09/2020), 13PBS211 (exp 01/2022), 13PMS152 (exp 11/2022), 13RHS141 (exp 07/2024) and 13RIF011 (exp 08/2024.

9. Duration of Treatment

Each patient received a single dose of either SGM-101 or Saline, 4 days (±1 day) prior to surgery.

10. Statistical Methods

A fixed-sequence method was used for controlling the type one error rate while testing the primary endpoint (E1), the key secondary efficacy endpoint (E2) then the 4 following secondary endpoints E3, E4, E5, and E6. The test of hypotheses for endpoint Ei+1 only proceeded if the test of hypotheses for endpoint Ei was significant, using a 0.05 two-sided type one error rate. The sequence of tests stopped as soon as a test was not significant at the 0.05 two-sided level.

A subgroup analysis of patients undergoing debulking surgery followed or not by HIPEC (HIPEC Subgroup) was conducted, for:

- component E1.3 of the primary efficacy endpoint
- E2
- E3
- E6

The primary efficacy analysis consisted in comparing the primary endpoint E1 to the theoretical rate of 5%, with a two-sided type one error rate of 5%, using a one-sample proportion exact binomial test. The main analysis was repeated without using the central histopathology for the endpoint derivation. The main analysis was repeated on each of the 3 components of the primary endpoint: E1.1, E1.2, and E1.3. The initial primary endpoint P1 (proportion of patients who had at least one additional biopsy/resection identified under NIR but not under WL that were true positive) was analyzed similarly as the primary endpoint E1.

The key secondary efficacy analysis consisted in comparing the key secondary efficacy endpoint E2 to the theoretical rate of 5%, with a two-sided type one error rate of 5%, using a one-sample proportion exact binomial test. The main analysis was repeated without using the central histopathology for the endpoint derivation on the FAS population and on HIPEC subgroup.

The false detection rate E3 was compared to the theoretical rate of 25%. The false detection rate E3 was analyzed as described for the key secondary efficacy endpoint. The main analysis was also repeated, with and without using central histopathology for the endpoint derivation, on the FAS population and on HIPEC subgroup.

The clinical benefit rate E4 was compared to the theoretical rate of 0%. The clinical benefit rate E4 was analyzed as described for the key secondary efficacy endpoint.

The fluorescence-guided surgery (FGS) benefit over WL alone rate E5 was compared to the theoretical rate of 0%. The FGS benefit over WL alone rate E5 was analyzed as described for the key secondary efficacy endpoint.

The analyses of the diagnostic performance of FGS were conducted within the SGM-101 arm only.

- The sensitivity (Se) rate E6 was compared to the theoretical rate of 70%. The sensitivity rate E6 was analyzed as described for the key secondary efficacy endpoint. The main analysis was at the resection level. The main analysis was also repeated, with and without using central histopathology for the endpoint derivation, on the FAS population and on HIPEC subgroup.
- The false positive rate (FPR) E7 was analyzed using descriptive statistics only. The main analysis was at the resection level. The main analysis was repeated without using the central histopathology for the endpoint derivation.
- The positive predictive value (PPV), negative predictive value (NPV), specificity (Sp) ratio, and accuracy rate, were analyzed as described for the FPR E7 endpoint.
- In addition, the diagnostic performance of FGS was analyzed on the subgroup of patients with fresh frozen section (FFS) taken during surgery.

The analysis of the tumor-to-background ratio (TBR) was conducted within the SGM-101 arm only. Descriptive statistics were computed by resection level for malignant zones only (using central histopathology).

The analysis of the impact of SGM-101 injection on the surgical procedure was conducted within the SGM-101 arm only. Descriptive statistics of the answers to the different items of the surgeon's questionnaire were tabulated by tumor location/type.

Descriptive statistics were computed for the pharmacokinetics (PK) variables for the SGM-101 arm.

Descriptive statistics were computed for positivity of anti-drug antibodies (ADA) (qualitative) and log-transformed dilution titers for ADA expressed as dilution factors (quantitative) at each time point.

Adverse events (AEs) were coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of starting the coding activities and were classified by MedDRA preferred term (PT) and system organ class (SOC). AEs were tabulated and presented by severity and causal relationship to IP and surgery for all patients included in the safety (SAF) and, if relevant (if the 2 populations differed) on the safety-surgery (SAF-Surg) analysis set.

Clinical laboratory values were summarized using descriptive statistics and listed. If relevant, shift figures comparing baseline value (Day -4) and value at the Day 5 visit were presented for each hematology, hemostasis, and biochemistry parameter. To facilitate the exploration of potential drug-induced liver injury, eDISH plots, displaying peak total bilirubin level versus peak ALT level, were presented.

Vital signs values, electrocardiogram (ECG) findings, and physical examination findings were summarized using descriptive statistics and listed.

An interim analysis was to be conducted after 180 patients had been randomized and had reached the Day 28 follow-up visit. This interim analysis aimed at stopping the study for futility, in case the observed results suggested that the probability of demonstrating a detection rate of SGM-101 greater than 5% with the planned sample size of 240 patients in the SGM-101 arm was too low.

The futility decision was based on comparing the conditional power of the study at the time of the interim analysis (computed under the initial alternative hypothesis of a 10% detection rate) to the pre-specified threshold of 45% (i.e., stopping any study for futility if the conditional power is less or equal to 45%).

The futility boundary was non-binding. This was specified in both the protocol, version 4.2, dated 30 Sep 2023 and the in the DMC charter, and was computed for both E1 (the actual primary endpoint) and P1 (the initially defined primary endpoint).

11. Summary of Results

11.1. Interim Analysis Results

The interim analysis was conducted in September 2023 based on 180 patients randomized.

The analysis was performed on the DMC3 Primary Estimand population, which included 135 patients in the SGM-101 arm, 103 patients (76.3%) in open surgery and 32 patients (23.7%) in laparoscopic surgery, and without using centrally reviewed histopathology.

The observed rates were 3.7% for E1 and 5.2% for P1. These results were obtained in open surgeries only.

Based on these interim results, the Data Monitoring Committee (DMC) members agreed that there was no benefit in continuing recruitment in the study as evidence at this stage indicated the study to be futile for the primary endpoint. However, they concluded that there were some interesting findings in the secondary endpoints which could be considered in designing future studies, particularly in view of the evolutions of technology in this field. There were no safety concerns raised at this review (DMC minutes of meeting available upon request).

In light of these conclusions, and in the absence of any safety signals or concerns related to the investigational product, the sponsor made the decision to terminate the study earlier than initially planned, but after the enrollment of a limited number of additional patients. The objective was to accumulate data in view of future studies and to evaluate the performance of a new laparoscopic imaging system (Karl Storz) in replacement of the previously utilized laparoscopic system (Quest Medical Imaging).

11.2. Patient Disposition

A total of 242 patients were randomized in the study (193 in the SGM-101 arm, and 49 in the saline arm). Of these, 223 patients received study treatment (177 in the SGM-101 arm, and 46 in the saline arm), 219 received study treatment and underwent surgery (173 in the SGM-101 arm, and 46 in the saline arm), and 212 completed the study (168 in the SGM-101 arm, and 44 in the saline arm).

All randomized and treated patients were included in the SAF analysis set (SGM-101: 177; saline: 46). Four patients in the SGM-101 arm were treated but did not undergo surgery. Thus, the full analysis set (FAS) and SAF-Surg analysis set comprised 173 patients in the SGM-101 arm and 46 in the saline arm. The FAS (Primary Estimand) included 160 patients in the SGM-101 arm.

11.3. Demography and Baseline Characteristics

Within the SAF analysis set, the mean age of the patients was 60.49 years, and 62.8% were males. Almost all patients were White (94.0%). The main tumor locations/types were cT3/4 rectal cancer and cT4 colon cancer (80 [35.9%] and 48 [21.5%] patients, respectively). Open surgery was planned in 172 (77.8%) patients (136 [77.7%] in the SGM-101 arm, and 36 [78.3%] in the saline arm), and laparoscopic surgery in 49 (22.2%) patients (39 [22.3%] in the SGM-101 arm, and 10 [21.7%] in the saline arm). Peritoneal metastasis procedure consisting of debulking surgery followed or not by HIPEC, was planned in 40 (17.9%) patients (32 [18.1%] in the SGM-101 arm, and 8 [17.4%] in the saline arm).

11.4. Efficacy Results

The observed rate for the primary endpoint exceeded the predefined threshold (E1>5%), however the difference was not statistically significant and did not allow to reject the null hypothesis.

In the HIPEC subgroup, the observed rate of the component E1.3 also exceeded 5%, however the result did not achieve statistical significance.

In addition, the observed rate of the initial primary endpoint P1 exceeded the 5% threshold, but the result did not reach statistical significance.

The secondary endpoints were hierarchically subordinated to endpoint E1. Thus, as the primary endpoint E1 did not meet the pre-established success criterion, the secondary evaluation criteria must be considered exploratory, even though nominal statistical significance was observed for all of them.

Nominal statistical significance was observed for the key secondary endpoint: conservative surgery benefit rate E2 both in the FAS population and in the HIPEC subgroup. However, these results were considered exploratory due to the hierarchical structure of the testing.

Nominal statistical significance was also observed for the false detection rate E3with a p-value of 0.0015, however the result was considered exploratory due to the hierarchical structure of the testing.

The observed rate of the clinical benefit rate E4 was higher than the target value (H0: E4=0%) with a p-value <0.0001. Although nominal statistical significance was observed, the result was considered exploratory due to the hierarchical structure of the testing.

The observed rate of the benefit of FGS over WL alone E5 was also higher than the target value (H0: E5=0%) with a p-value <0.0001. However, although nominal statistical significance was observed, the result was considered exploratory due to the hierarchical structure of the testing.

For all endpoints, analyses by stratification factors did not highlight any trends or differences for any geographical region or tumor location/type.

For all endpoints, the sensitivity analyses conducted without central histopathology were consistent with the main analyses.

The mean TBR of the core lesion evaluated on the backtable was higher than the one for the core lesion in vivo before resection. The mean TBRs were highest in the core lesion wound bed and core lesion histology.

A total of 142 completed surgeon's questionnaires were collected. In one third of the responses, the technology was reported to provide added value in assisting tumor localization. In nearly half of the questionnaires the surgeons survey highlighted the utility of this technique when performing surgery, in spite of the low quality of the camera system that was used in laparoscopic procedures. In a majority of questionnaires, surgeons reported no discomfort, found image acquisition time acceptable, and considered the system easy to use with interpretable images. Additionally, more than 70% expressed interest in using the technology more frequently in the future.

11.5. Pharmacokinetic Results

Analysis of PK data after single injection of SGM-101 showed that SGM-101 was rapidly absorbed, reaching Cmax in 2.88 hours, and slowly eliminated, with mean terminal half-life of 82.22 hours.

11.6. Immunogenicity Results

ADAs were low or absent across most patients, with only 5 patients positive for neutralizing antibody throughout the study. No impact on fluorescence nor on pharmacokinetics, and no safety concerns were observed for these patients.

11.7. Safety Results

Treatment-emergent Adverse Events

In the SAF analysis set, 175 (78.5%) patients had at least 1 TEAE during the study: 140 (79.1%) patients in the SGM-101 arm and 35 (76.1%) patients in the saline arm.

The most common TEAEs were abdominal pain (38 [17.0%] patients), nausea (38 [17.0%] patients), hypokalemia (27 [12.1%] patients), and procedural pain (25 [11.2%] patients overall), with frequency comparable across arms.

Most TEAEs were graded mild (Grade 1) or moderate (Grade 2). Sixty-six patients (29.6%) experienced at least 1 TEAE of at least severe intensity (≥Grade 3) (49 [27.7%] in the SGM-101 arm and 17 [37.0%] in the saline arm).

TEAEs related to the study treatment were rare, reported only in the SGM-101 arm in 9 (5.1%) patients, and consisted mainly of nausea (4 [2.3%] patients) and headache (2 [1.1%] patients).

TEAEs related to the surgical procedure were reported in 169 (75.8%) patients: 134 (75.7%) patients in the SGM-101 arm and 35 (76.1%) patients in the saline arm. The most common TEAEs related to the surgical procedure were abdominal pain, nausea, hypokalemia, and procedural pain.

No TEAEs led to study treatment infusion discontinuation. TEAEs leading to study discontinuation were rare (2 [0.9%] patients) and comparable across arms.

Surgery-emergent Adverse Events

In the SAF analysis set, 171 (76.7%) patients had at least 1 Surg-EAE during the study: 136 (76.8%) patients in the SGM-101 arm and 35 (76.1%) patients in the saline arm.

The most common Surg-EAEs were nausea (37 [16.6%] patients), abdominal pain (33 [14.8%] patients), hypokalemia (27 [12.1%] patients), and procedural pain (24 [10.8%] patients), with frequency comparable across arms.

Most Surg-EAEs were graded mild (Grade 1) or moderate (Grade 2). Sixty-four patients (28.7%) experienced at least 1 Surg-EAE of at least severe intensity (≥Grade 3) (47 [26.6%] in the SGM-101 arm and 17 [37.0%] in the saline arm)

Surg-EAEs related to the study treatment were infrequent, reported only in the SGM-101 arm in 6 (3.4%) patients, and consisted mainly of nausea (4 [2.3%] patients).

Surg-EAEs related to the surgical procedure were reported in 168 (75.3%) patients: 133 (75.1%) patients in the SGM-101 arm and 35 (76.1%) patients in the saline arm. The most common Surg-EAEs related to the surgical procedure were nausea, abdominal pain, hypokalemia, and procedural pain.

No Surg-EAEs led to study treatment infusion discontinuation.

Surg-EAEs leading to study discontinuation were rare (1 [2.2%] patient in the saline arm).

Serious Adverse Events

SAEs were reported in 56 (25.1%) patients during the study: 45 (25.4%) patients in the SGM-101 arm and 11 (23.9%) patients in the saline arm. None of them were considered as related to the study treatment, while they were considered as related to the surgical procedure in 45 (20.2%) patients: 35 (19.8%) patients in the SGM-101 arm and 10 (21.7%) patients in the saline arm.

There were 3 deaths during the study, 1 (0.6%) in the SGM-101 arm and 2 (4.3%) patients in the saline arm that were considered as related to the surgical procedure.

Other Safety Assessments

No relevant changes from baseline to Day 5 were observed for any vital signs, ECG parameters, physical findings, or routine laboratory parameters in either study arm.

12. Overall Conclusions:

In this Phase 3 clinical study, SGM-101 was evaluated as an intraoperative near-infrared fluorescence imaging agent intended to support detection and resection of CEA-expressing

colorectal cancer lesions. While the overall population did not show a statistically significant improvement in the primary composite endpoint, the HIPEC subgroup displayed a consistent trend toward clinical benefit, with a success rate higher than that observed in the FAS, supporting further investigation in this specific population.

Secondary endpoints showed encouraging signals, including improved conservative surgery benefit, in particular in the HIPEC subgroup of eligible patients, and overall clinical benefit rates. However, due the prespecified hierarchical testing procedure for the primary and secondary endpoints to control the overall type I error rate, these exploratory findings cannot be considered confirmatory but may guide future clinical development and study design.

SGM-101 showed a favorable safety profile consistent with prior clinical studies. No new safety concerns emerged. Pharmacokinetic behavior was predictable with stable exposure profiles following a single 10 mg intravenous dose. Anti-drug antibodies were detected in a small number of patients only, including some with pre-existing antibodies. In addition, among the confirmed ADA-positive samples, only a limited number demonstrated neutralizing activity. PK and ADA results thus support the predictability of systemic exposure with the current 10 mg dosing regimen administered four days prior to surgery and reinforce the favorable tolerability profile observed throughout the study.

The initial laparoscopic NIR imaging system used in the study has shown limitations including insufficient sensitivity and suboptimal resolution, which likely reduced fluorescence detection in minimally invasive procedures. Recruitment delays and early termination led to a smaller sample size than planned, which constrained statistical power and the interpretability of the results.

Although confirmatory efficacy was not achieved, the exploratory signals observed in multiple secondary endpoints, together with the favorable safety profile and biological rationale, support further evaluation of SGM-101, particularly in selected patient subgroups such as those undergoing debulking surgery followed or not by HIPEC and in conjunction with more advanced (laparoscopic) NIR imaging systems.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the concentration vs. time curve
CEA	carcino-embryonic antigen
CI	confidence interval
Cmax	maximum concentration
CRO	Contract Research Organization
CS	clinically significant
cT3/4	clinical stage T3/4
cT4	clinical stage T4
D	day
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full analysis set
FDA	Food and Drug Administration
FFS	fresh frozen section
FGS	fluorescence-guided surgery
FN	false negative
FP	false positive
FPR	false positive rate
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPEC	hyperthermic intraperitoneal chemotherapy
HIV	human immunodeficiency virus
HR	heart rate
IB	investigator’s brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

IND	Investigational New Drug
IP	investigational product
MedDRA	Medical Dictionary for Regulatory Activities
NaCl	sodium chloride
NIR	near-infrared
NPV	negative predictive value
PK	pharmacokinetic(s)
PPV	positive predictive value
PT	preferred term
Q	quartile
QTc	corrected QT
SAE	serious adverse event
SAF	safety
SAF-Surg	safety-surgery
SAP	statistical analysis plan
SOC	system organ class
Surg-EAE	surgery-emergent adverse event
Surg-ESAE	surgery-emergent serious adverse event
T½	terminal half-life
TBR	tumor-to-background ratio
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
Tmax	time to maximum concentration
TN	true negative
TP	true positive
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization-Drug Dictionary
WL	white light

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