

An acoustic coupling fluid improves intraoperative ultrasound image quality during glioma surgery: Results of a Pivotal Multicenter Study (NCT04734444)

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Article

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Title

An acoustic coupling fluid improves intraoperative ultrasound image quality during glioma surgery: Results of a Pivotal Multicenter Study (NCT04734444)

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Abbreviations:

ACF – Acoustic Coupling Fluid

CI – Confidence Interval

CNR – Contrast-to-Noise Ratio

DMC – Data Monitoring Committee

EDC – Electronic Data Capture

ioUS – Intraoperative Ultrasound

mITT – Modified Intention-to-Treat

MRI – Magnetic Resonance Imaging

SAE – Serious Adverse Event

SIR – Surgeon Image Rating

SD – Standard Deviation

Abstract

Intraoperative ultrasound uniquely provides repeatable, real-time guidance throughout glioma resection without interrupting surgery. However, image quality deteriorates at resection completion, when imaging is most critical: irrigation fluids attenuate ultrasound less than brain tissue, producing hyperechoic artefacts beneath the cavity that obscure or mimic residual tumour. Existing operator-dependent strategies do not correct this mismatch. Here, we show that SonoClear, a tissue-mimicking acoustic coupling fluid, reduces these artefacts and improves interpretability. In a prospective, non-randomised study at five centres, 44 patients received SonoClear and 40 contributed to paired comparisons with standard irrigation fluid. SonoClear reduced below-cavity artefactual signal (ratio of contrast-to-noise ratios, irrigation/SonoClear: 1.70; 95% CI, 1.48–1.95). Five independent neurosurgeons masked to the fluid reported a mean paired Surgeon Image Rating improvement of 1.96 points (95% CI, 1.80–2.11). No serious adverse events were judged probably or definitely device-related within 30 days; postoperative magnetic resonance imaging showed no major findings in 36 evaluated patients. These findings support acoustic matching to improve ultrasound guidance, including at resection completion; effects on resection extent and patient outcomes require investigation.

1. Introduction

Image guidance is a cornerstone of modern oncological neurosurgery. Multiple intraoperative modalities are available. Besides neuronavigation, intraoperative ultrasound (ioUS) remains the most widely used in routine practice. IoUS, including navigated, 3D, and multimodal implementations, provides real-time, repeatable imaging that fits naturally into the surgical workflow, with a comparatively low infrastructural burden (Jenkinson et al. 2018). Evidence supporting clinical benefit is growing: for instance, a randomized controlled trial in glioblastoma reported higher rates of complete resection of contrast-enhancing tumour with B-mode ioUS guidance compared with standard navigation, without worsening patient-centred outcomes (F et al. 05/19/2021). More broadly, reviews and reports highlight that ioUS can help maximize resection, although comparative effectiveness and the optimal “standard package” vary across settings (M et al. 12/03/2018; B et al. 05/09/2022; AV and P 2016 Mar; A et al. 04/01/2020; F et al. 05/19/2021; Sæther et al. 2012).

A persistent challenge, especially when resection control matters most, as in intra-axial (e.g. glioma) tumours, is the interpretability of ultrasound images late in the resection (Dixon et al. 2022; A et al. 03/22/2021; T et al. 2013 Jun). Surgically induced artefacts can dominate the intra-resection view, obscure subtle residual tumour, and increase ambiguity along the cavity wall and in deeper regions. These limitations have been described across tumour types and ioUS workflows and include an “enhancement” pattern driven by a physical mismatch between the fluid filling the resection cavity and the surrounding brain tissue (Dixon et al. 2022; A et al. 03/22/2021; T et al. 2013 Jun) (Figure 1). Selbekk et al. proposed that the dominant surgically induced ioUS artefact results from the attenuation mismatch between saline in the resection cavity and surrounding brain tissue. This artificially amplifies echoes from deeper structures, creating a hyper-echogenic region beneath the cavity that can obscure or mimic residual tumour, thereby reducing confidence in image interpretation (Dixon et al. 2022; A et al. 03/22/2021; T et al. 2013 Jun).

Several technical measures may partially mitigate these issues, including choice of probe, scanning technique, navigated co-registration, or close-up insonation from within the cavity. Each approach comes with workflow and learning-curve trade-offs, and none fully addresses the underlying physics of cavity-related artefact formation (G et al. 2006 Mar; A et al. 03/22/2021; T et al. 2013 Jun; G et al. 2019 Jul). This limitation prompted the development of SonoClear® acoustic coupling fluid (ACF), a tissue-mimicking medium designed to match the acoustic properties of brain tissue and reduce cavity-related artefacts. In a phase I clinical feasibility study, an early prototype reduced image noise compared with standard Ringer’s solution while demonstrating an acceptable safety profile, supporting further clinical evaluation. (G et al. 2019 Jul). This pivotal multicentre ACF-03 investigation evaluates a late prototype (SC-ACF-1001), of the SonoClear® System, with identical tissue mimicking properties.

In the pivotal multicentre ACF-03 investigation (registered as NCT04734444), each patient was subjected to paired intraoperative acquisitions with standard sterile irrigation fluid and with SonoClear® ACF. The image pairs were collected at prespecified near-end resection timepoints, with performance assessed using

both quantitative and qualitative image-quality endpoints. The present manuscript reports the clinical performance and safety findings from this pivotal study.

2. Methods

2.1. Study design and participants

ACF-03 was a prospective, multicentre, non-randomised, within-patient controlled pivotal clinical investigation conducted at five tertiary neurosurgical centres in Italy, Germany, and Slovakia. The study evaluated the safety and image-performance of SonoClear® acoustic coupling fluid (ACF), a sterile, tissue-mimicking ultrasound coupling fluid developed to reduce resection-cavity artefacts during intraoperative ultrasound (ioUS)-guided resection of suspected de novo gliomas. Each participant served as their own control through paired intraoperative ultrasound acquisitions performed with standard sterile irrigation fluid followed by SonoClear ACF. The study was registered at ClinicalTrials.gov (NCT04734444).

Participating centres were IRCCS Fondazione Istituto Neurologico Carlo Besta (Milan, Italy), University Hospital Ulm (Ulm, Germany), University Hospital Bratislava/Comenius University (Bratislava, Slovakia), Schwarzwald-Baar Klinikum (Villingen-Schwenningen, Germany), and Philipps University Marburg (Marburg, Germany). Recruitment was conducted between Sept 12, 2021, and June 21, 2023, and the final study follow-up was completed on Dec 30, 2023.

Eligible participants were adults (≥ 18 years) undergoing ioUS-guided resection of a suspected de novo diffuse glioma, with histopathological confirmation obtained preoperatively or intraoperatively. Additional inclusion criteria included a Karnofsky Performance Status of at least 70 and an expected survival of more than 30 days. Women of childbearing potential were required to have a negative pregnancy test before surgery. Key exclusion criteria were previous cranial radiotherapy, active central nervous system or systemic infection, immunodeficiency or ongoing immunosuppressive therapy, planned biopsy without tumour resection, known hypersensitivity to any study-device component, and pregnancy or breastfeeding. All participants provided written informed consent before enrolment.

2.2. Intervention and imaging procedures

IoUS images were acquired at predefined intraoperative time points: (i) after craniotomy and dural opening (no fluids involved), (ii) at approximately 80% resection when residual tumour was expected in the deeper part of the cavity, and (iii) at surgeon-declared completion of resection. At the second and third time point, ioUS acquisition was performed twice, first with standard sterile irrigation fluid (Saline (0.9%) or Ringer's solution) and then with SonoClear® ACF, only minutes apart and at the same location within the resection cavity, with the ultrasound system settings optimized for the irrigation-fluid acquisition and kept fixed for the paired SonoClear® ACF acquisition, thereby enabling within-subject comparisons. The acquisition order was prespecified and not randomised to avoid carry-over effects. Once SonoClear® ACF had been introduced into the resection cavity, residual coupling fluid could not be reliably excluded despite aspiration and irrigation, potentially influencing subsequent ultrasound acquisitions performed with standard irrigation

fluid. Therefore, standard irrigation imaging was always completed before administration of SonoClear ACF. (Figure 1 and 2)

The SonoClear® ACF was removed immediately after the image acquisition, according to standardized procedural guidelines: the fluid was aspirated from the resection cavity, followed by a minimum of three irrigation-and-aspiration cycles using standard sterile irrigation fluid, and repeated until the cavity fluid appeared macroscopically clear. At the completion of this procedure, no SonoClear® ACF was macroscopically visible within the resection cavity. Accordingly, postoperative MRI was performed in the absence of visible residual SonoClear® ACF.

Image evaluations for quantitative analysis were performed in a blinded fashion, and paired image sets could be presented in random order with respect to the applied fluid.

2.3. Outcomes

The primary safety endpoint was the proportion of subjects experiencing a primary safety event within 30 days, with the event defined as either: (i) a core-lab determined major postoperative MRI finding versus preoperative MRI that the Data Monitoring Committee (DMC) deemed serious and probably/definitely related to the device, or (ii) a DMC-determined serious adverse event (SAE) probably/definitely related to the device. Secondary safety assessment comprised a full accounting of adverse events at 30 days and via a 6-month follow-up call, with events contextualized against expected rates for this surgical population. Postoperative complications were collected (including grading using the Landriel Ibañez classification) and MRI findings were assessed according to the study schedule.

Performance was assessed using two complementary co-primary endpoints: quantitative assessment of below-cavity artefact burden using contrast-to-noise ratio (CNR), and qualitative assessment using the Surgeon Image Rating (SIR).

1) Contrast-to-noise ratio (CNR). CNR was the quantitative co-primary endpoint and was measured by an independent core laboratory on paired intraoperative ultrasound images acquired at the two predefined resection-control timepoints (approximately 80% tumour resection and surgeon-declared end of resection). A predefined region of interest immediately beneath the resection cavity was analysed to quantify below-cavity artefactual signal. Higher CNR values indicated greater artefactual signal enhancement, whereas lower values indicated reduced artefact burden. Treatment effects were expressed as the ratio of standard irrigation fluid to SonoClear® ACF CNR; therefore, ratios greater than 1 indicate lower artefactual signal with SonoClear® ACF.

2) Surgeon Image Rating (SIR): SIR was the qualitative co-primary endpoint and consisted of a 10-point rating scale evaluating (1) differentiation between brain tissue and tumour in deeper regions, (2) interpretability beneath the resection cavity, and (3) confidence in identifying possible residual tumour. SIR assessments were performed independently by the operating surgeon immediately after image acquisition

and by an independent panel of five experienced neurosurgeons (each with ≥ 3 years of intraoperative ultrasound experience), who evaluated all image pairs while masked to the coupling fluid used.

2.4. Follow-up and data quality

Clinical follow-up was conducted at approximately 72 hours and 30 days postoperatively, with an additional follow-up call at 6 months. Data were captured in an electronic data capture (EDC) system via a secure web portal with restricted access; data management procedures included programmed and manual consistency/plausibility checks and query resolution, with analyses conducted according to a prespecified Statistical Analysis Plan.

2.5. Sample size rationale

Sample size justification was based on pilot (phase I) data. For CNR, the pilot study reported a mean ratio (standard irrigation fluid / SonoClear® ACF prototype) of 1.68 with SD 1.35; analyses were planned on the log scale, and the pivotal study was powered to detect an effect size of ~ 0.77 (log scale), providing $\geq 90\%$ power at a 5% significance level with 20 subjects meeting modified intention-to-treat (mITT) criteria. For SIR, the study was powered to detect an effect size of ~ 0.83 (corresponding to an approximate mean paired difference of 1.5 SIR units assuming SD 1.8), providing $\geq 90\%$ power at a 5% significance level with 18 mITT subjects. For safety, observing 0 primary safety events in 37 subjects provided $>90\%$ power (two-sided type I error 5%) using the exact 95% confidence interval framework.

2.6. Statistical analysis

Safety analyses included all participants who received SonoClear® ACF (Safety Set). Performance analyses were performed in the modified intention-to-treat population, comprising participants with histologically confirmed glioma and evaluable paired intraoperative ultrasound images. All analyses were performed using SAS version 9.4.

For the primary safety endpoint, the proportion of participants experiencing a device-related primary safety event within 30 days was estimated with exact two-sided 95% confidence intervals and compared with the prespecified safety threshold of 10%. Adverse events were summarised according to seriousness and relationship to the device or procedure. The two co-primary performance endpoints were analysed using a hierarchical gatekeeping procedure: CNR superiority was tested first; if significant, SIR was subsequently tested while preserving an overall two-sided type I error of 5%.

CNR was analysed using repeated-measures linear mixed-effects models accounting for paired measurements within participants and repeated intraoperative timepoints. Treatment effects were expressed as the ratio of standard irrigation fluid to SonoClear® ACF, with ratios greater than 1 indicating lower artefactual signal with SonoClear® ACF. Prespecified covariates included centre, tumour grade, age, sex,

tumour location, ultrasound system, probe type, and acquisition timepoint. SIR was analysed using repeated-measures linear mixed-effects models with paired within-subject comparisons across raters, questions, and acquisition timepoints. Prespecified covariates mirrored those used for the CNR analyses. Covariates significant at $p < 0.10$ in univariable analyses were entered into multivariable models including two-way interactions, followed by backward elimination.

All statistical tests were two-sided, and p values < 0.05 were considered statistically significant unless otherwise specified.

2.7. Ethics

The study protocol was approved by the institutional review board or independent ethics committee at each participating centre before study initiation and was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines (ISO 14155), and all applicable national regulatory requirements. All participants provided written informed consent before enrolment and before undergoing any study-specific procedures. An independent Data Monitoring Committee (DMC) oversaw participant safety throughout the study and adjudicated serious adverse events and MRI safety findings according to the prespecified protocol.

2.8. Role of the funding source

The study was funded by SonoClear AS, which provided financial support for the conduct of the trial. The sponsor had no role in patient recruitment, clinical management, surgical decision-making, image acquisition, image interpretation, endpoint assessment, or clinical follow-up.

3. Results

3.1. Study population and baseline characteristics

Overall, 45 patients were enrolled and 44 underwent the index procedure and constituted the Safety Set; one patient was excluded because of possible contamination of the comparator. All 44 patients completed the 72-hour and 30-day follow-up visits. Of these, 40 patients were included in the modified intention-to-treat population, as they had biopsy-confirmed glioma and a set of interpretable images for each of the performance outcomes. Patients were recruited across five centers (Milan 18/44, 40.9%; Ulm 12/44, 27.3%; Bratislava 9/44, 20.5%; Marburg 1/44, 2.3%; Schwarzwald 4/44, 9.1%).

Mean age was 51.3 years (SD 15.6), and 33/44 (75.0%) patients were male. High-grade tumours accounted for 29/44 (65.9%), while 15/44 (34.1%) were low-grade. Gross-total resection was achieved in 18/43 (41.9%) cases; the mean extent of resection was 90.9% (SD 11.0; median 95.0). Baseline, tumour, and operative characteristics of the treated cohort are summarized in Table 1.

3.2. Safety

Primary safety endpoint: postoperative MRI (≤ 72 h)

No participant experienced the prespecified primary safety endpoint. No device-related serious adverse event and no device-related major MRI finding occurred within 30 days of surgery.

Paired pre- and postoperative MRI assessments were available for 36 patients. Across all evaluated brain areas, no major MRI findings were identified. Minor findings (e.g., cortex/meninges changes near the surgical opening) were common and were adjudicated as expected postoperative changes; notable findings were observed in a minority (e.g., parenchyma: 5/36 [13.9%] on DWI; 6/36 [16.7%] on T2/Flair) and were also considered expected postoperative findings.

Consistent with these observations, the report concludes that the primary safety event rate criterion was met (0 observed events, with an upper two-sided 95% confidence limit below 10%).

Adverse events (30 days) and serious adverse events

Within the Safety Set (n=44), a total of 37 adverse events (including serious adverse events) were reported in 24 patients (54.5%). Three events in three patients (6.8%) were assessed by investigators as possibly related to SonoClear® ACF; all three were serious adverse events (postoperative epileptic seizure, hydrocephalus at day 99, and an intracranial infection), and each was also considered likely procedure-related (probable/causal).

Procedure-related adverse events accounted for 30 events in 21 patients (47.7%), most commonly epileptic seizures (6 events in 4 patients, 9.1%) and hematoma (4 events in 3 patients, 6.8%).

Mortality and longer follow-up

All patients were alive at 30 days (30-day mortality 0%). Three deaths occurred beyond 30 days (two within 6 months and one at 202 days post-procedure); all were assessed as related to tumor progression rather than device or procedure.

At 6 months, 39/44 (88.6%) completed follow-up; events reported at 6 months (including deaths) were not considered related to SonoClear® ACF. Overall safety outcomes are summarized in Table 2.

3.3. Performance

Performance was evaluated using complementary quantitative (CNR) and qualitative (SIR) endpoints. Both demonstrated consistent superiority of SonoClear® ACF over standard irrigation fluid.

Quantitative image performance

Contrast-to-noise ratio (CNR) was assessed by the Core Lab at two intraoperative time points (80% of planned resection and surgical-defined end of resection, sdER). In descriptive analyses, mean CNR values were lower with SonoClear® ACF than with standard sterile irrigation fluid at both time points (80%: 37.0 [SD 23.4] vs 66.5 [SD 47.2]; sdER: 37.2 [SD 21.6] vs 75.2 [SD 49.4]), corresponding to irrigation/SonoClear® ACF ratios of 1.86 and 2.02, respectively. Since the ratio was calculated as standard irrigation fluid divided by SonoClear® ACF, values above 1 indicate that CNR was higher with irrigation and therefore reflect a relative reduction in sub-cavity artefactual enhancement with SonoClear® ACF.

In the mixed-effects model, SonoClear® ACF was associated with a significantly improved CNR ratio versus standard irrigation fluid, with an estimated average irrigation/SonoClear® ACF ratio of ~1.70 (95% CI 1.48–1.95; $p < 0.001$). The image-quality endpoints, including CNR results, are summarized in Table 3.

Qualitative image performance

On the 1–10 scale Surgeon Image Rating (SIR) values favored SonoClear® ACF across all three questions (overall image quality, tumour border delineation, and residual tumour detection) at both assessed time points. For example, at 80% resection, mean SIR with SonoClear® ACF ranged from 6.85–6.92 versus 4.56–5.15 with standard irrigation fluid; at sdER, mean SIR with SonoClear® ACF ranged from 6.99–7.09 versus 4.76–5.16 with standard sterile irrigation fluid.

In the Core-Lab mixed model, the estimated average paired improvement with SonoClear® ACF was 1.955 points (95% CI 1.802–2.108; $p < 0.001$). Representative examples of the corresponding image-quality improvement are shown in Figure 2.

Taken together, the concordant quantitative reduction in artefactual signal and qualitative improvement in image interpretability provide complementary evidence supporting the image-performance of SonoClear® ACF during glioma surgery.

4. Discussion and conclusions

This pivotal clinical investigation provides evidence on the safety and clinical performance of SonoClear® ACF as an acoustic coupling fluid during ioUS-guided resection of de novo gliomas. In 44 treated subjects with follow-up up to 6 months, SonoClear® ACF consistently improved ioUS image quality, by reducing artefactual noise below the resection cavity, while maintaining an acceptable perioperative safety profile.

Safety evaluation combined Core-Lab comparison of pre-operative and early post-operative (~72 h) MRI with adjudication of SAEs within 30 days. The report indicates that all MRI findings were expected postoperative outcomes; no major MRI findings were reported, and none were surely attributed to SonoClear® ACF. None of the observed SAEs were judged probably or definitely related to SonoClear® ACF. Benchmarking of event frequencies against literature-derived ranges further supported that the overall adverse-event pattern was consistent with the state of the art for glioma resection, without evidence of an excess complication rate. At 6 months, recorded events were not related to SonoClear® ACF, and deaths during follow-up were attributed to tumour re-progression.

Clinical performance was assessed using two co-primary endpoints: CNR, and SIR. Compared with standard coupling media used in routine practice (Sterile Saline (0.9%) or Ringer's solution), SonoClear® ACF demonstrated superior reduction of below-cavity noise, corresponding to an approximately 1.7-fold improvement in CNR-based noise reduction within the prespecified region of interest below the resection cavity. Importantly, the quantitative gains translated into improved interpretability of ioUS images. Notably, these improvements were observed not only by the operating surgeons, who were necessarily aware of the intervention, but also by an independent panel of experienced neurosurgeons who evaluated the image pairs while masked to the coupling fluid used. This concordance between unblinded intraoperative assessments and blinded independent review strengthens the robustness of the qualitative findings and suggests that the observed improvements are unlikely to be explained solely by observer expectation or procedural bias. Importantly, these improvements were confirmed both by the operating surgeons and by an independent expert panel blinded to the coupling fluid used. This agreement between intraoperative and blinded assessments strengthens the robustness of the qualitative findings and reduces the likelihood that the observed benefit reflects observer expectation alone. Mixed-effects modelling supported statistical superiority versus irrigation fluids across these items, with the improvement in residual-tumour assessment reported to be greater than the improvement in interpretation below the cavity, an observation of relevance given the clinical challenge of distinguishing true residual tissue from artefact in the post-resection field.

In glioma surgery, in which maximal safe resection is a central therapeutic objective because it is associated with improved oncological outcomes. To this end, ioUS has the unique ability to provide repeatable, real-time imaging throughout tumour removal, from initial localisation to progressive assessment and final resection control. However, reliable imaging is needed most near the end of resection, precisely when surgically induced cavity artefacts may obscure or mimic small residual tumour and reduce confidence in pursuing further resection. Technical strategies such as probe selection, optimisation of scanning trajectories, navigated co-registration, or close-up insonation from within the cavity can partially mitigate these artefacts, but remain operator-dependent, may require workflow adaptations, and do not correct the underlying acoustic mismatch between standard irrigation fluid and brain tissue. By replacing the conventional coupling fluid with a tissue-mimicking medium, SonoClear® ACF directly addresses this mechanism without altering the surgical workflow. In this study, it significantly reduced below-cavity

artefactual signal and improved the interpretation of tumour borders and possible residual tumour, while maintaining an acceptable perioperative safety profile. Although its effects on extent of resection and patient outcomes remain to be established prospectively, these findings indicate that SonoClear® ACF addresses a key practical limitation of ioUS at the stage when accurate imaging may improve patients outcomes.

Limitations include that the study was designed around imaging performance and safety rather than downstream oncologic or functional outcomes (e.g., extent of resection, progression-free survival, overall survival, neurological morbidity). Therefore, although CNR and SIR provide complementary quantitative and qualitative evidence of improved intraoperative image interpretability, they remain imaging surrogate endpoints, and further studies are needed to determine whether these improvements translate into measurable benefits in surgical decision-making and patient-level outcomes. In addition, the acquisition order of the two fluids was fixed, with standard sterile irrigation fluid always assessed before SonoClear® ACF. Although the fixed acquisition order was necessary to avoid carry-over of the coupling fluid, an order effect cannot be completely excluded and should be considered when interpreting the magnitude of the treatment effect. Finally, the investigational product used in this cohort differs from the subsequently updated SonoClear® System (packaging and formulation refinements, but with identical tissue mimicking properties), and the study included adults only; therefore, additional clinical evidence is warranted to confirm performance and safety of updated configurations and to inform use in younger populations.

Future prospective studies should specifically evaluate whether the improved intraoperative image interpretability provided by SonoClear® ACF can influence surgical decision-making, for example by revealing surgically accessible residual tumour after surgeon-declared completion of resection with standard irrigation fluid and ultimately translate into higher extent of resection or improved patient-level outcomes.

In conclusion, this study supports that SonoClear® ACF provides statistically superior reduction of ioUS artefact and improved interpretability for intraoperative decision-making compared with standard sterile irrigation fluids, while maintaining an acceptable safety profile. Future studies and post-market follow-up should connect these imaging benefits to patient-level outcomes and extend evaluation to updated product configurations.

Contributors

MDB, GC, JC, AS, RR, BS, FD, and FDM conceived and designed the study. MDB, GC, JC, AS, RR, and BS enrolled participants and acquired the clinical and intraoperative imaging data. MDB, GC, FD, and FDM interpreted the data. MDB and GC accessed and verified the underlying participant-level data. MDB, GC, JC, AS, RR, performed the literature review and drafted the first version of the manuscript. All authors critically revised the manuscript for important intellectual content, approved the final version for publication, and accept responsibility for the accuracy and integrity of the work.

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Declaration of interests

The study was funded by SonoClear AS. The sponsor provided financial support for the study and supplied the investigational device. The sponsor had no role in patient recruitment, clinical management, surgical decision-making, image acquisition, image interpretation, endpoint assessment, clinical follow-up, interpretation of the study findings, or the decision to submit the manuscript for publication.

All authors declare no competing interests.

Role of the funding source

The study was funded by SonoClear AS. The sponsor supported study conduct and operational trial management according to the prespecified protocol but had no role in patient recruitment, clinical care, surgical decision-making, image acquisition, image interpretation, endpoint assessment, or interpretation of the study findings. Statistical analyses were performed according to the prespecified Statistical Analysis Plan. The authors had full access to the study data. MDB and GC verified the underlying participant-level data. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Data sharing

Deidentified individual participant data underlying the results reported in this Article, together with the study protocol, statistical analysis plan, and data dictionary, will be available beginning 12 months and ending 5 years after publication to researchers whose proposed use has been approved by an independent

review committee and who sign an appropriate data-access agreement. Requests should be directed to the corresponding author at [francesco.dimeco@istituto-besta.it]. Data availability remains subject to applicable ethical, legal, institutional, and contractual requirements.

Use of artificial intelligence

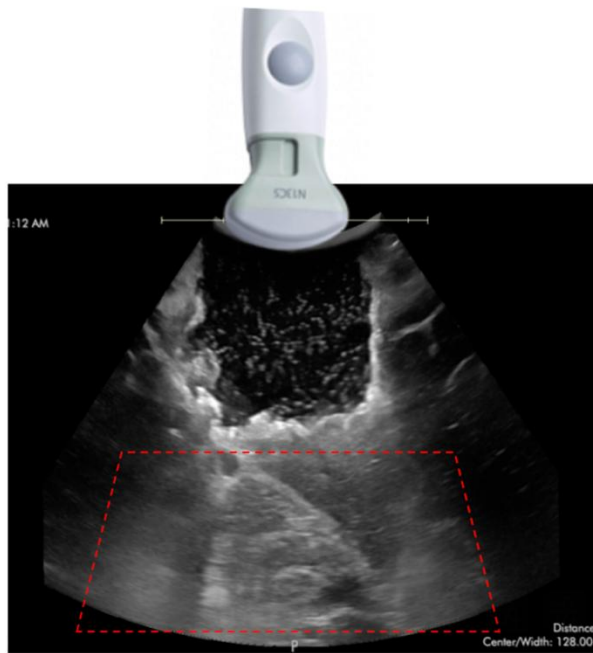
Generative artificial intelligence (ChatGPT, OpenAI GPT-5.5) was used to assist with language editing, restructuring of the manuscript, and improvement of clarity and readability. The authors critically reviewed, verified, and edited all AI-assisted content and take full responsibility for the final manuscript, including the accuracy, interpretation, and integrity of all reported data and conclusions.

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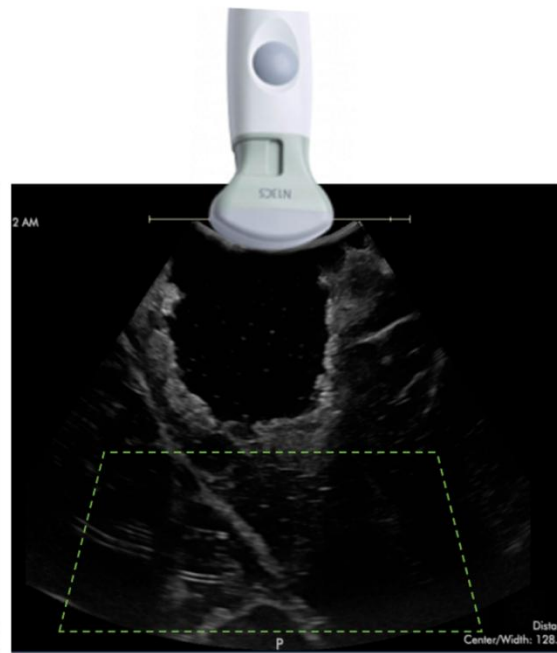
Figures and tables Legend

A Standard irrigation fluid



Acoustic noise degrades image quality

B SonoClear



Reduced acoustic noise improves cavity-floor visualisation

Figure 1. Reduction of cavity-related ultrasound artefacts with SonoClear® ACF. Paired intraoperative ultrasound images illustrate the effect of replacing standard sterile irrigation fluid with SonoClear® acoustic coupling fluid (ACF) within the resection cavity. Standard irrigation fluid is associated with artifacts below-cavity, reflecting acoustic noise generated by mismatch between the cavity fluid and adjacent brain tissue. SonoClear® ACF reduces this artefactual enhancement, improving visualization of the cavity floor and deeper parenchyma.

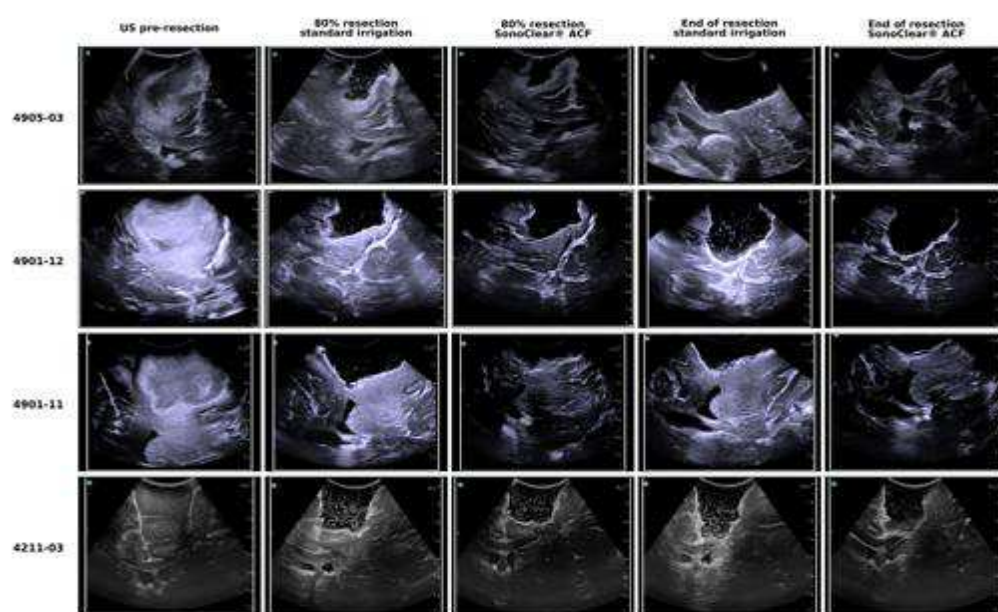


Figure 2. Paired intraoperative ultrasound acquisitions showing reduced cavity-related artefacts with SonoClear® ACF. Four representative cases are shown at the predefined intraoperative imaging time points: pre-resection ultrasound after craniotomy without fluid, approximately 80% resection, and surgeon-declared end of resection. At the 80% and end-of-resection time points, paired acquisitions were obtained first with standard sterile irrigation fluid, saline 0.9% or Ringer’s solution, and then with SonoClear® ACF, using fixed ultrasound settings. Standard irrigation was associated with hyperechogenic enhancement beneath the resection cavity, which may obscure the cavity floor and complicate assessment of residual tumour. After replacement with SonoClear® ACF, the below-cavity artefact was visibly reduced, improving delineation of the cavity floor and adjacent parenchyma and supporting more confident assessment of whether echogenic tissue represented true residual tumour or artefactual enhancement.

Characteristic	Value
Enrolled patients	45
Safety set / index procedure with SonoClear® ACF	44
Completed 30-day follow-up	44/44 (100%)
Recruiting centre: Milan	18/44 (40.9%)
Recruiting centre: Ulm	12/44 (27.3%)
Recruiting centre: Bratislava	9/44 (20.5%)

Recruiting centre: Schwarzwald-Baar	4/44 (9.1%)
Recruiting centre: Marburg	1/44 (2.3%)
Age, years	51.3 ± 15.6
Male sex	33/44 (75.0%)
High-grade glioma	29/44 (65.9%)
Low-grade glioma	15/44 (34.1%)
Gross-total resection	18/43 (41.9%)
Extent of resection, %	90.9 ± 11.0; median 95.0

Table 1. Baseline and operative characteristics of the treated cohort. Values are n/N (%) or mean ± SD unless otherwise stated. This table summarizes the Safety Set and the key operative variables relevant to interpretation of the performance and safety endpoints.

Safety domain	Result	Interpretation
Primary safety endpoint within 30 days	0 primary safety events observed	Prespecified safety criterion met
Core-lab MRI assessment ≤72 h	36 paired MRI assessments; no major MRI findings	Observed changes were adjudicated as expected postoperative findings
Any adverse event	37 events in 24/44 patients (54.5%)	Observed frequency was broadly consistent with the expected morbidity profile of glioma resection.
Investigator-assessed possible device-related AEs	3 events in 3/44 patients (6.8%)	All were also considered likely procedure-related; none were fatal
Procedure-related AEs	30 events in 21/44 patients (47.7%)	Most common: epileptic seizure and hematoma
Serious adverse events	Reported SAEs were not judged probably/definitely related to SonoClear® ACF by the DMC	No device-related SAE signal above the prespecified threshold
30-day mortality	0/44 (0%)	No early mortality
Six-month follow-up	39/44 completed follow-up (88.6%); No late device-related	No late device-related safety signal identified

	safety signal was identified during available follow-up	
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Table 2. Safety outcomes. Safety was assessed using early postoperative MRI, adverse-event reporting through 30 days, and a 6-month follow-up call. The primary safety endpoint was met, with no probably or definitely device-related serious adverse event and no device-related major MRI finding within 30 days. DMC, Data Monitoring Committee; MRI, magnetic resonance imaging; SAE, serious adverse events

Endpoint / timepoint	Standard irrigation fluid	SonoClear® ACF	Paired effect	Inference
CNR at ~80% resection	66.5 ± 47.2	37.0 ± 23.4	Irrigation/SonoClear ratio 1.86	Lower CNR with SonoClear® ACF indicates reduced subcavity artefact burden
CNR at surgeon-defined end of resection	75.2 ± 49.4	37.2 ± 21.6	Irrigation/SonoClear ratio 2.02	Consistent reduction in subcavity artefactual signal at end of resection
CNR mixed- effects model	-	-	Estimated ratio 1.70 (95% CI 1.48-1.95); p<0.001	Co-primary quantitative endpoint met
Independent expert SIR mixed-effects model	-	-	Mean paired difference +1.955 points (95% CI 1.802-2.108); p<0.001	Co-primary qualitative endpoint met
Operating- surgeon SIR, ~80% resection	4.56-5.15	6.85-6.92	Favours SonoClear® ACF across all three questions	Higher interpretability, tissue differentiation and residual-tumour confidence

Operating- surgeon SIR, end of resection	4.76-5.16	6.99-7.09	Favours SonoClear® ACF across all three questions	Consistent surgeon-perceived improvement at final resection control
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Table 3. Co-primary image-quality endpoints comparing SonoClear® ACF with standard sterile irrigation fluid. CNR values are mean $\pm$ SD. The mixed-model CNR result is expressed as an irrigation/SonoClear® ratio; therefore, a ratio greater than 1 indicates that paired standard-irrigation images had higher below cavity artefact burden than SonoClear® ACF images. SIR is reported on a 1-10 scale, with positive paired differences favouring SonoClear® ACF. ACF, acoustic coupling fluid; CI, confidence interval; CNR, contrast-to-noise ratio; SIR, Surgeon Image Rating.