Trials

STUDY PROTOCOL

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6-mm vs 10-mm diameter fully covered self-expandable metal stents in patients with unresectable malignant distal bile duct stricture (COSMIC UNISON): study protocol for a multicenter, randomized controlled trial

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Abstract

Background Unresectable malignant bile duct stricture (often caused by unresectable pancreatic cancer and cholangiocarcinoma) can be drained via insertion of self-expandable metal stents (SEMS) during endoscopic retrograde cholangiopancreatography (ERCP). Because recurrent biliary obstruction (RBO) and complications following stent insertion can delay chemotherapy and other treatments, a longer time to RBO (TRBO) is desirable. Although a longer TRBO has been reported among patients who undergo insertion with larger diameter SEMS, patients who undergo insertion with smaller diameter fully covered SEMS (FCSEMS) may have a lower incidence of complications than those with larger diameter FCSEMS. The aim of this study is to determine the TRBO and incidence of complications with 6-mm FCSEMS vs 10-mm FCSEMS in patients with unresectable malignant distal bile duct stricture.

Methods In this multicenter, open-label, randomized controlled, non-inferiority trial (COSMIC UNISON), a target of 250 patients over 23 locations in Japan will receive either the 6-mm FCSEM or the standard 10-mm FCSEM during ERCP, with 125 patients in each group. The observation period will be 24 months, and patients will be enrolled from 15 March 2024 and assessed until the date of RBO or the study end (31 March 2029). The primary endpoint is TRBO, with RBO defined as the coexistence of abnormal liver enzyme values and dilation of the common bile duct and intrahepatic bile duct upstream of the stent. The secondary endpoints are the incidence and rates (at 3, 6,

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and 12 months) of non-RBO events, overall survival, cause of RBO, and symptomatic stent deviation. Adverse events from endoscopic procedures will be classified by the Lexicon Classification from the American Society of Endoscopy, and all other adverse events will be classified per the Japanese translation of the Common Terminology Criteria for Adverse Events version 5.0.

Discussion The COSMIC UNISON study is anticipated to provide evidence regarding the efficacy and safety of 6-mm vs 10-mm FCSEMS to inform the use of 6-mm FCSEMS for the treatment of unresectable malignant distal bile duct stricture.

Trial registration Japan Registry of Clinical Trials identifier: jRCT1042230170. Prospectively registered on 15 March 2024.

Keywords Endoscopic retrograde cholangiopancreatography, Malignant distal bile duct stricture, Recurrent biliary obstruction, Self-expandable metal stents

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	6-mm vs 10-mm diameter fully covered self-expandable metal stents in patients with unresectable malignant distal bile duct stricture (COSMIC UNISON): study protocol for a multicenter, randomized controlled trial
Trial registration {2a and 2b}	jRCT1042230170
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Name and contact information for the trial sponsor {5b}	M.I.Tech Co., Ltd., the Mie University Hospital Specific Clinical Research Incentive Fund, and operating grants from the Department of Gastroenterology and Hepatology, Mie University Hospital Inae Kim Tel: +82 70 4304 7450 Email: inae116@mitech.co.kr
Role of sponsor {5c}	The sponsors had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Introduction

Background and rationale {6a}

Malignant biliary strictures are often caused by unresectable pancreatic cancer and cholangiocarcinoma [1, 2]. These strictures can be drained via the insertion of self-expandable metal stents (SEMS), and this often occurs during endoscopic retrograde cholangiopancreatography (ERCP). SEMS with a longer time to recurrent biliary obstruction (TRBO) are preferable, and patients who undergo insertion of SEMS with a larger diameter are reported to have a longer TRBO [3]. The 2017 European Society of Gastrointestinal Endoscopy guidelines recommend the use of SEMS that are 10 mm in diameter [4].

In 2019, a prospective comparative study of patients with malignant distal bile duct stricture found no difference in TRBO between 8-mm and 10-mm diameter fully covered SEMS (FCSEMS) [5]. Additionally, this study

reported no difference in the incidence of SEMS-related complications [5]. A recent retrospective comparative study of 6-mm and 10-mm diameter FCSEMS also reported no significant difference in TRBO between the two stent sizes [6]. Moreover, the group who received 6-mm stents had a lower incidence of complications associated with SEMS implantation than the 10-mm group (11.4% [19/167] vs 31.6% [24/76]; $p < 0.01$) [6].

However, as the reported incidence of accidental injury with stent implantation varies [7–14], a multicenter study is necessary to determine whether the incidence of complications is lower with 6-mm stents vs 10-mm stents. Furthermore, to our knowledge, there have been no reported prospective comparative studies of 6-mm and 10-mm diameter FCSEMS in patients with unresectable malignant distal bile duct stricture. Therefore, this trial will be conducted to address this evidence gap and to inform the use of 6-mm FCSEMS.

Objectives {7}

The objective of this study is to compare the TRBO and frequency of complications (such as cholecystitis and pancreatitis) in Japanese patients with unresectable malignant distal bile duct stricture treated with either 6-mm or 10-mm diameter FCSEMS to determine non-inferiority.

Trial design {8}

This study is a multicenter, randomized controlled, non-inferiority trial (COSMIC UNISON) in which eligible patients will receive either the 6-mm diameter FCSEMS or the standard 10-mm diameter FCSEMS during ERCP (Fig. 1).

Methods: participants, interventions, and outcomes

Study setting {9}

The study will be conducted in Japan, across 23 locations. The participating institutions and investigators are listed in Table 1.

Eligibility criteria {10}

Eligible patients will be aged ≥18 years and have unresectable malignant distal bile duct stricture of ≥2 cm distal to the confluence of the right and left hepatic ducts; a confirmed diagnosis of malignancy by tissue analysis; and abnormal serum total bilirubin (>1.5 mg/dL), aspartate aminotransferase (AST; >100 IU/L), alanine transaminase (ALT; >100 IU/L), gamma-glutamyltranspeptidase (γ-GTP; >150 IU/L), or alkaline phosphatase (ALP) levels (>250 IU/L) requiring endoscopic drainage per the International Federation of Clinical Sciences criteria.

Patients undergoing biliary drainage with a metal stent, resectable cancer per the pancreatic cancer resectability classifications resectable (R), borderline resectable invading the portal vein (BR-PV), or borderline resectable abutting major arteries (BR-A) [15], Eastern Cooperative Oncology Group performance status (ECOG-PS) of 4, postoperative reconstruction of the upper gastrointestinal tract (excluding Billroth I reconstruction), dysfunction of other organs (American Society of Anesthesiologists physical status classification grade III or IV), life expectancy ≤3 months (this ensures that included patients are expected to survive the duration of the study), and those pregnant or possibly pregnant will be excluded. These criteria were designed to include patients with established indications that require the use of metal stents in the distal bile duct as well as those who would likely benefit from the intervention.

Endoscopists eligible for performing the procedure will be those who have ≥10 years' experience with ERCP, or those supervised by endoscopists with ≥10 years' experience with ERCP.

Who will take informed consent? {26a}

Using easy-to-understand language, the Principal Investigator and investigators at each participating institution will provide explanation in writing and orally to each potential trial participant and obtain voluntary informed consent in writing. Informed consent will be obtained in a calm, private environment to ensure there will be no disturbances. Patients will be given adequate time to consider their decision and will be allowed to have a companion present during the consent process. For eligible patients who are physically unable to provide written informed consent, verbal informed consent confirmed by a witness may be noted in the consent form.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable; no additional participant data or biological specimens will be collected. Separate approval from the Ethics Review Committee will be sought prior to any secondary use of non-identifiable data obtained in this study.

Interventions

Explanation for the choice of comparators {6b}

To evaluate whether 6-mm FCSEMS are as effective as 10-mm FCSEMS for the treatment of patients with unresectable malignant distal bile duct stricture, we will compare outcomes of patients who receive 6-mm diameter FCSEMS vs those who receive 10-mm diameter FCSEMS. Adverse events will also be compared.

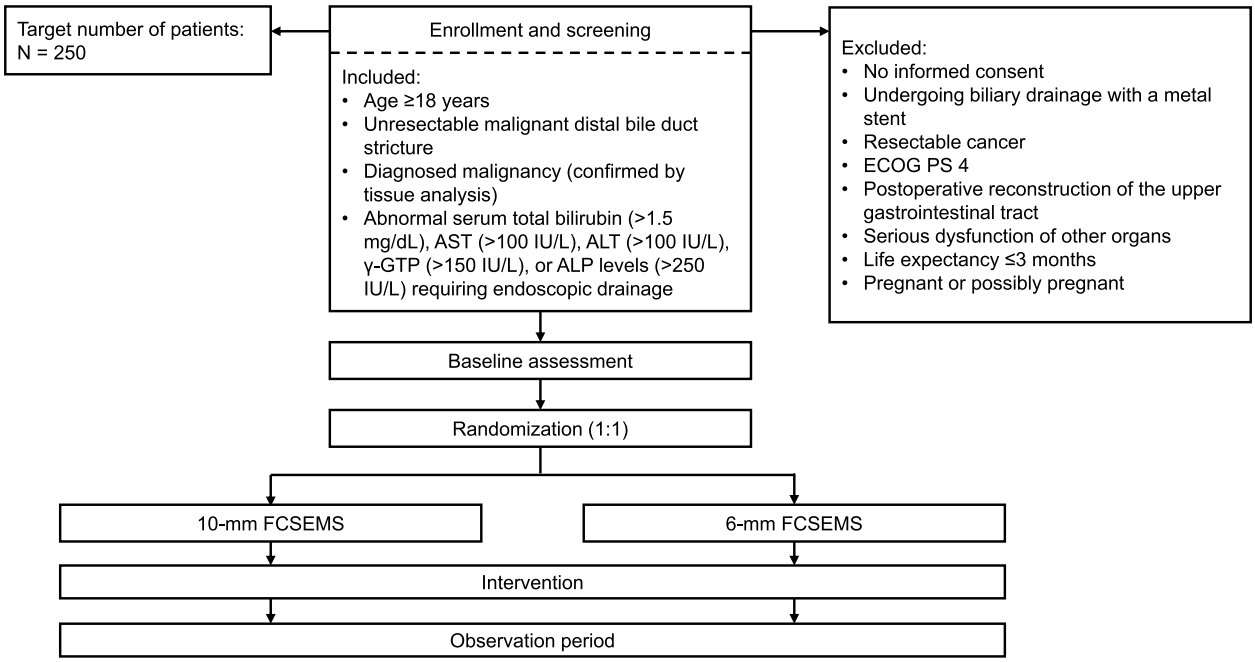

Fig. 1 COSMIC UNISON flow diagram. γ-GTP, gamma-glutamyltranspeptidase; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; ECOG-PS, Eastern Cooperative Oncology Group performance status; FCSEMS, fully covered self-expandable metal stents

Intervention description {11a}

Patients will be randomized to receive either the standard treatment (a HANAROSTENT® Biliary Full Cover NEO 10 mm Diameter Full Cover [Boston Scientific, Natick, MA, USA]) or the intervention (HANAROSTENT® Biliary Full Cover Benefit Full-Coverage 6 mm diameter [Boston Scientific, Natick, MA, USA]) (Fig. 1). The stent length will be long enough to cover ≥10 mm upstream from the stenosis and to allow the lower end of the stent to exit ≥5 mm toward the duodenum from the papilla. Patients should undergo the procedure within 14 days of enrollment; if a patient receives the treatment later than 15 days, the reason will be noted.

Criteria for discontinuing or modifying allocated interventions {11b}

Discontinuation can occur in the following situations: the patient requests withdrawal or withdraws consent; if it is found that eligibility is not satisfied after registration; inability to continue examinations for illness or other reasons; discovery of a pregnancy; failure to visit the hospital; or any other situation where the physician considers it appropriate to discontinue the study. Patients that meet any of the exclusion criteria will be identified and excluded prior to study entry. Thus, patients who do not meet the eligibility requirements will not be randomized.

Strategies to improve adherence to interventions {11c}

Not applicable, because the intervention is applied once during the ERCP procedure.

Relevant concomitant care permitted or prohibited during the trial {11d}

Patients can receive antispasmodics, sedatives, and analgesics during the procedure, as required. Patients may also receive the following concomitant and supportive therapies: diclofenac or other pancreatitis prophylaxis, prophylactic antibiotics, prophylactic hemostatic agents such as carbazochrome sodium sulfonate or tranexamic acid, pancreatic duct stenting for the prevention of pancreatitis, and endoscopic biliary drainage with guidewire-assisted insertion via a percutaneous transhepatic bile duct puncture route or with guidewire-assisted insertion via an ultrasound endoscopic puncture route.

Provisions for post-trial care {30}

As medical care provided in this study will be covered by the patients' insurance coverage, no additional compensation for medical expenses or other care post-trial will be provided.

Outcomes {12}

The primary endpoint is TRBO, defined as the time (days) between the date of registration and the occurrence of recurrent biliary obstruction (RBO). RBO is defined as

Table 1 Participating institutions and investigators

Study site	Name of participating medical institution	Investigator name
1	Shizuoka Cancer Center	Junya Sato
2	Shizuoka General Hospital	Shinya Kawaguchi
3	Kanazawa Medical University Hospital	Tsuyoshi Mukai
4	Gifu Municipal Hospital	Keisuke Iwata
5	Gifu Prefectural Tajimi Hospital	Fumihiro Okumura
6	Gifu General Medical Center	Akinori Maruta
7	Hamamatsu University Hospital	Ken Sugimoto
8	Aichi Medical University Hospital	Tadahisa Inoue
9	Nagoya University Hospital	Hiroki Kawashima
10	Fujita Medical University Hospital	Yoshiki Hirooka
11	Aichi Cancer Center	Kazuo Hara
12	Kumamoto University Hospital	Motohiro Yoshinari
13	Kumamoto City Hospital	Shunpei Hashigo
14	Seirei Hamamatsu Hospital	Yosuke Kobayashi
15	Mie University Hospital	Reiko Yamada
16	Kagawa University Hospital	Hideki Kamada
17	Kuwana City General Medical Center	Yumi Oya
18	Yokkaichi Hazu Medical Center	Shigehito Nakashima
19	Suzuka Kaisei Hospital	Shunsuke Tano
20	Saiseikai Matsusaka General Hospital	Akira Hashimoto
21	Matsusaka Chuo General Hospital	Hiroaki Naota
22	Okanami General Hospital	Hajime Imai
23	Ise Red Cross Hospital	Toji Murabayashi

the coexistence of abnormal liver enzyme values from blood tests and the observation of dilation of the common bile duct and intrahepatic bile duct upstream of the stent on imaging tests (abdominal ultrasound, computer tomography scan, magnetic resonance imaging, or ERCP) [16]. Abnormal liver enzyme values are defined as total bilirubin (>1.5 mg/dL), AST (>100 IU/L), ALT (>100 IU/L), γ-GTP (>150 IU/L), or ALP levels (>600 IU/L). The date of RBO occurrence is defined as the date when the bile duct dilation is observed, not the time of symptom onset.

The secondary safety endpoint is the incidence of non-RBO events, including pancreatitis, non-stent obstructive cholangitis, cholecystitis, bleeding, perforation, and other events (for example, ulceration) [16].

Secondary efficacy endpoints are non-RBO rates (at 3, 6, and 12 months), overall survival, cause of RBO (stent obstruction [tumor ingrowth or mucosal hyperplasia, tumor overgrowth, biliary mud with or without concomitant stones], presence of food residue, biliary bleeding, bile duct kink, or other), and symptomatic stent deviation (liver side or papillary side).

The background information that will be collected are patient age, sex, ECOG-PS, type of primary disease (pancreatic cancer, cholangiocarcinoma, gallbladder cancer, papillary carcinoma, lymph node metastasis, or unknown), histological diagnosis, degree of progression (local/metastatic, TNM classification [17]), resectability classification (per the pancreatic cancer treatment protocol for pancreatic cancer [15]), presence/absence of duodenal invasion, presence/absence of gallbladder enlargement (per the Guidelines for the Treatment of Acute Cholangitis [18]), presence and type of immediate bile duct drainage, presence and severity of acute cholangitis (per the Guidelines for the Treatment of Acute Cholangitis [18]), peripheral blood count, and biochemical test results (white blood cell, platelet count, total bilirubin, AST, ALT, ALP, γ-GTP, C-reactive protein, and amylase).

Participant timeline {13}

The schedule of enrollment, interventions, and assessments is shown in Table 2.

Sample size {14}

The target sample size is set at 250 patients (125 patients per group). A Japanese retrospective comparative study of stents for malignant distal bile duct stricture reported an RBO rate at 12 months of 52.4% and 43.5% in the 10-mm and 6-mm groups, respectively [6]. Thus, the

Table 2 Observation schedule

	Enrollment	Date of treatment[a]	Observation period (months)			End[b]
			3	6	12	
Informed consent	●					
Eligibility screen	●					
Allocation		●				
Interventions						
6-mm diameter FCSEMS		●				
10-mm diameter FCSEMS		●				
Assessments						
Patient background	●					
Type of immediate bile duct drainage	●					
Presence and severity of acute cholangitis	●					
Peripheral blood count and biochemical tests	●					
Details of bile duct stenting procedure, prophylaxis use, and surgeon experience in ERCP		●				
Time to RBO						●
Clinical success						●
Blood tests			Every 3 months, until RBO occurs			
Imaging studies			As needed			
Non-RBO rate			●	●	●	
Overall survival						●
Presence of anti-tumor therapy						●
Adverse events other than RBO						●
Information on discontinuation			At any time			

ERCP endoscopic retrograde cholangiopancreatography, *FCSEMS* fully covered self-expandable metal stents, *RBO* recurrent biliary obstruction

[a] Within 14 days of enrollment

[b] Date of RBO or study end (31 March 2029)

median expected TRBO for the 10-mm group and the 6-mm group in this study is set at 9 months.

The non-inferiority margin is a hazard ratio (HR) of 1.33. With a one-sided α of 0.05 and a detection power of 80%, the target number of patients is set to 250, assuming that approximately 5% of patients will be ineligible.

The enrollment period is set to 36 months, and the observation period will be 24 months. Approximately one patient every 2 months in ≥20 participating institutions is expected over 36 months; therefore, over 360 eligible patients are expected to be enrolled. Assuming consent will be obtained from 80% of these patients, a target population of 250 patients is considered feasible.

Recruitment {15}

Investigators at each institution will create a list of all patients presenting with unresectable malignant distal bile duct stricture regardless of their requirement for interventional treatment. Investigators will screen patients on the list for eligibility. The Principal Investigator will create a webpage to introduce the current trial to hospitals so as to increase referral rate.

Assignment of interventions: allocation

Sequence generation {16a}

Patient background data will be submitted to the web-based Nagoya University Registration & Randomization System (NaRRS) to ascertain eligibility and for randomization to the two treatment groups.

Concealment mechanism {16b}

Not applicable; no concealment or blinding methods will be used as this is an open-label trial.

Implementation {16c}

The Principal Investigator or Associate Investigator will enter the patient data into the NaRRS and review the entered data. The NaRRS will then randomly allocate patients to the two treatment groups, adjusting for confounding factors such as primary disease type (pancreatic cancer or non-pancreatic cancer), gallbladder enlargement (presence or absence), and pre-drainage (presence or absence). Details of the randomization

procedure will only be known by the data center and will not be made available to investigators.

Assignment of interventions: blinding

Who will be blinded {17a}

Not applicable; no blinding methods will be used as this is an open-label trial.

Procedure for unblinding if needed {17b}

Not applicable; no blinding methods will be used as this is an open-label trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All data will be collected using an electronic case report form after each visit and submitted online to NaRRS.

Plans to promote participant retention and complete follow-up {18b}

All patients will be followed up until the occurrence of RBO or the end of the study. The standard follow-up period will be every 3 months; however, the observation method will not be specified, and it will be acceptable to obtain and evaluate data provided by other centers. If a patient has transferred to another hospital or does not attend visits for other reasons, it will be permissible to confirm the outcome by telephone, and information provided by other hospitals will be included in the electronic medical record.

Data management {19}

To maintain data integrity, the Principal Investigator will ensure that the trial is conducted appropriately, including the generation, recording, and reporting of data, and will implement a quality control and quality assurance system. The data center checks the data entry status and other information and informs each medical facility for quality control.

Confidentiality {27}

The Principal Investigator will be responsible for ensuring confidentiality of data and for preserving all data relating to the study for at least 5 years from the date of the report on the completion of the study.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Blood samples will be collected for outcome assessments, but no protocols will be specified regarding their collection or storage. No other biological specimens will be collected as part of this study, and no genetic or molecular analyses will be conducted.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Considering that the aim of the study is to compare the outcomes of 6-mm and 10-mm FCSEMS following ERCP, the primary analysis for the primary endpoint will be the full analysis set (FAS). The primary analysis for the secondary efficacy endpoint will be the intention-to-treat (ITT) set, and the safety analysis set (SAS) will be analyzed regarding the secondary safety endpoints. Additionally, the FAS will be analyzed for the secondary efficacy endpoint to confirm the stability of the analysis result.

The FAS will comprise all patients who receive the intervention and the stent is implanted, and for whom the primary endpoint is evaluated. The ITT set will include all enrolled patients. The SAS will include all patients who receive the intervention, regardless of whether the stent is implanted.

Mean values and their standard deviation will be calculated for continuous variables; for ordinal variables, frequency distribution tables will be created. Mean values for each group will be compared using Student's *t*-test, and frequencies will be compared using a chi-square test or Fisher's exact test.

For the primary endpoint, the HR for the 6-mm group to the 10-mm group will be estimated using a 95% confidence interval (CI) corresponding to a one-sided significance level of 5%. CIs will be calculated using the Wald method, and non-inferiority will be judged as the upper limit of the 95% CI for the HR not exceeding the null hypothesis (HR: 1.33). Survival will be analyzed using a competing risk analysis, and a log-rank test will be conducted to compare survival between groups. Factors associated with RBO or with other events will be analyzed using univariate and multivariate analyses of the background characteristics, intraoperative examination data, and postoperative evaluation data.

Multiple imputation will be employed as the primary method for handling missing outcome data. This approach allows missing values to be replaced with a set of plausible values that reflect the natural variability of the data. Multiple imputed datasets will be generated, analyzed separately, and then combined to produce a single, robust estimate while accounting for the uncertainty associated with missing data. Additionally, sensitivity analyses will be conducted to assess how different methods of handling missing data influence the results. This will include comparisons between multiple imputation and simpler methods including listwise deletion.

The significance level will be 5% one-sided for the primary endpoint, and the significance level will be 5% two-sided for all other analyses. All statistical analyses will be

conducted using Easy R version 1.65 (Jichi Medical University Saitama Medical Center) [19].

Interim analyses {21b}

Methods for additional analyses (e.g., subgroup analyses) {20b}

No interim analyses will be performed.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Analysis will occur on the entire population (with no data excluded from the analyses) and cases with missing data will not be excluded. In cases of protocol non-adherence, the Principal Investigator will submit the details and reasons for protocol deviation to the Clinical Research Review Committee.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The full protocol and datasets generated and/or analyzed during the study will be available after publication from the Principal Investigator on reasonable request.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The trial steering committee consists of the Principal Investigator (R.Y.), Co-Principal Investigator (T.T.), and a representative from the investigator team at each center. The Clinical Research Support Center at Mie University Hospital will act as the coordinating center for this trial. The Clinical Research Review Committee will advise on the conduct of the trial, including approval and revisions to study documents and approval of any changes to the protocol.

Composition of the data monitoring committee, its role and reporting structure {21a}

Data monitoring will be conducted by an individual who is not directly involved in the implementation of the research. Additionally, an Efficacy and Safety Evaluation Committee will be established and convened in accordance with the requests of the Clinical Research Review Committee, in the case of significant changes to the research protocol, occurrence of serious events, issues with monitoring, or other times as deemed necessary by the Principal Investigator. All clinical research-related records will be provided by the Principal Investigator during monitoring, audits, and investigations related to the trial.

Adverse event reporting and harms {22}

Adverse events will be defined as an unfavorable or unintended symptom, sign, or laboratory finding that occurs after the study intervention. All adverse events, regardless of the causal relationship to the intervention, will be recorded. However, pre-existing conditions (for example, minor illnesses such as the common cold or abnormal laboratory values) with an onset prior to the intervention will not be reported.

Adverse events from endoscopic procedures will be classified by the Lexicon Classification from the American Society of Endoscopy [16]. All other adverse events will be classified per the Japanese translation of the Common Terminology Criteria for Adverse Events version 5.0 (Japan Clinical Oncology Group Shared Criteria Scope) [20]. Adverse events that meet one of the following criteria will be defined as serious adverse events: those leading to death, those that are life-threatening, those requiring hospitalization or prolongation of hospitalization, those resulting in permanent or marked disability or dysfunction, or those that cause birth defects in offspring. If a causal relationship between an event with the intervention is established and an urgent report is considered necessary, the Principal Investigator will report the case to the Japan Ministry of Health, Labour and Welfare.

Frequency and plans for auditing trial conduct {23}

Monitoring will be conducted by an independent monitor who is not related to the study, at a frequency of at least once a year through central monitoring to confirm that the trial is being conducted safely and in accordance with the protocol, and that data are collected appropriately. Additionally, the trial will be monitored in the event of serious illness, discontinuations, or other important events. If deviations from the implementation plan are discovered, an audit may be conducted.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Amendments to the protocol may only be made after review and approval by the Clinical Research Review Committee. Amendments must also be approved by the director of the medical institutions involved in the study, and the Japan Ministry of Health, Labour and Welfare will be advised of the change to the implementation plan. After approval has been obtained, the Principal Investigator will communicate the amendments to each of the individuals involved in the research (including other investigators and the data center).

Dissemination plans {31a}

The results of the trial, both positive and negative, will be reported at international conferences and/or published in an international journal.

Discussion

The COSMIC UNISON multicenter, randomized controlled trial will investigate whether 6-mm FCSEMS are as effective as 10-mm FCSEMS for the treatment of patients with unresectable malignant distal bile duct stricture, and whether 6-mm FCSEMS have a lower frequency of complications. The main causes of unresectable malignant bile duct stricture (unresectable pancreatic cancer and cholangiocarcinoma) are often either treated with chemotherapy or patients are transferred to palliative care as prognosis is poor [21–24]. Stents that have a longer patency and result in fewer complications are particularly desirable in these patients as the delayed initiation of chemotherapy and other treatment because of complications (including pancreatitis or cholecystitis) may further shorten the prognosis [6].

Previous studies have suggested that FCSEMS with smaller diameters may be as effective as the recommended 10-mm diameter stents and have fewer complications [5, 6]. This multicenter study is anticipated to provide further evidence regarding the efficacy and safety of 6-mm FCSEMS vs 10-mm FCSEMS and may inform the use of 6-mm FCSEMS for the treatment of unresectable malignant distal bile duct stricture.

The limitations of this study include the study locations, which are all in Japan. This may limit the generalizability of the findings to other countries. Additionally, the open-label design of the study creates a risk of potential bias. However, as the diameter of the stents will be different sizes, it is not possible to conduct a blinded trial of these interventions. Despite these limitations, this trial is anticipated to provide evidence for the use of 6-mm FCSEMS, with its multicenter design serving as a key strength of the study.

In conclusion, the COSMIC UNISON trial will aim to clarify whether 6-mm stents are as effective as 10-mm stents, and whether they are less likely to result in complications, in patients with unresectable malignant distal bile duct stricture.

Trial status

The current version of the protocol is 1.3, which was updated on 23 December 2023. The recruitment started on 1 May 2024 and is scheduled to be completed on 31 March 2026. The study will be terminated on 31 March 2029 or when the presence or absence of RBO is confirmed in all patients.

Abbreviations

γ-GTP	Gamma-glutamyltranspeptidase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BR-A	Borderline resectable abutting major arteries
BR-PV	Borderline resectable invading the portal vein
CI	Confidence interval
ECOG-PS	Eastern Cooperative Oncology Group performance status
ERCP	Endoscopic retrograde cholangiopancreatography
FAS	Full analysis set
FCSEMS	Fully covered self-expandable metal stents
HR	Hazard ratio
ITT	Intention-to-treat
NaRRS	Nagoya University Registration & Randomization System
R	Resectable
RBO	Recurrent biliary obstruction
SAS	Safety analysis set
SEMS	Self-expandable metal stents
TRBO	Time to recurrent biliary obstruction

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Authors' contributions {31b}

R.Y., Y.I., and T.T. contributed to the conception and design of the study. R.Y., T.T., and H.Nakagawa contributed to funding acquisition. R.Y. and T.T. wrote the original protocol. R.Y., T.T., Y.S., H.O., K.N., Y.N., T.Miwata, J.T., K.H., Y.Hamaya, S.Hashigo, A.H., S.Hijioka, Y.Hirooka, H.I., T.I., K.I., H.Kawashima, S.K., H.Kamada., Y.K., A.M., T.Mukai, T.Murabayashi, S.N., H.Naota, F.O., K.O., Y.O., J.S., K.S., S.Tano, and M.Y. were responsible for trial data and management. R.Y., T.T., T.O., Y.I., and S.Tamaru developed the statistical analysis plan. R.Y. wrote the paper. All authors reviewed and approved the paper.

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Data availability {29}

The full protocol and datasets generated and/or analyzed during the study will be available after publication from the Principal Investigator on reasonable request.

Declarations

Ethics approval and consent to participate {24}

The study will be conducted in accordance with the Declaration of Helsinki and the Japan Clinical Trials Act and all relevant national and international guidance for the conduct of human trials. The study was approved by the Ethics Review Committee (approval number S2023-001). Written informed consent will be obtained from all participants; verbal informed consent confirmed by a witness may be obtained from eligible patients who are unable to provide written consent.

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests.

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