**Study Protocol**

**Title:** Safety and efficacy of biodegradable biliary and pancreatic stents (ARCHIMEDES)

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**Study type:** A prospective study in 3 key indications at ERCP

**Aims:**

Primary aims:

* To assess the feasibility and safety of the novel bio-degradable stent (ARCHIMEDES) in three groups:
1. Duct to duct anastomotic strictures
2. Hepaticojejunal strictures
3. Post ERCP pancreatitis prophylaxis (PEP)

Secondary aims:

* To determine the degradation time of the stents observed by abdominal radiograph (X-ray)
* To assess the requirement for second procedure to remove the stent
* To assess the rate of stricture resolution (clinical)
* To determine the need for repeat stenting for stricture resolution

**Duration of the Study**: 3 years

**Ethics Statement:**

The study will be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (2007, updated 2018), the *CPMP/ICH Note for Guidance on Good Clinical Practice* and consistent with the principles that have their origin in the Declaration of Helsinki. Compliance with these standards provides assurance that the rights, safety and well-being of trial participants are respected.

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# Introduction

Biliary and pancreatic stents are used for the management of ductal obstruction. Currently, both stents are either made of a plastic or metal alloy. As a result, repeat endoscopic retrograde cholangio-pancreatography (ERCP) is required for stent removal. Whilst the cost of ERCP varies between countries, it is associated with a large economic burden to healthcare. Moreover, metal and plastic stents can occlude over a period of time due to formation of biofilm resulting in either recurrence of original symptoms due to stent blockage or additional complications. Biodegradable stents (ARCHIMEDES, manufactured by Amg International GmbH, Winsen, Germany, distributed in Australia by Endotherapeutics Pty Ltd) gradually degrade over a variable period of time and in theory can be used to treat ductal obstruction without requiring a repeat endoscopic procedure for stent retrieval1.

Biodegradable stents could represent a promising therapeutic option in the field of pancreatobiliary diseases, such as benign biliary (e.g. stricture post liver transplant patients) and pancreatic strictures post-cholecystectomy bile leaks and as a prophylaxis for post ERCP pancreatitis. Post-ERCP pancreatitis (PEP) is the most common complication of ERCP and can lead to significant morbidity as well as occasional mortality. In high-risk patients, several measures can be undertaken to limit the risk of PEP, including administration of rectal nonsteroidal anti-inflammatory drugs, liberal administration of lactated Ringer solution and importantly, temporary placement of pancreatic duct stent. In such cases, a repeat procedure is required to remove the stent.

In the last few years, feasibility and safety of endoscopic placement of different biodegradable biliary stents has been investigated in few pilot studies with promising outcomes2, 3 with one study using the aforementioned ARCHIMEDES biodegradable stent1. Our aim is to study the feasibility and safety of the novel bio-degradable stent (ARCHIMEDES) in 3 patient groups: (1) Post liver transplant duct to duct anastomotic strictures; (2) hepaticojejunostomy anastomotic strictures and (3) patients requiring post ERCP pancreatitis (PEP) prophylaxis with pancreatic stent placement. Thus far there have been no prospective studies assessing feasibility, safety and efficacy in these 3 patient groups.

# Hypothesis

We hypothesize that biodegradable stents are a safe and effective for the treatment of strictures in post liver transplant patients (duct to duct anastomosis and hepaticojejunostomy) and for PEP prophylaxis in patients undergoing ERCP

# Aims

## Primary aims (according to each of the above groups)

* To assess the feasibility and safety of the novel bio-degradable stent (ARCHIMEDES) in three groups:
1. Duct to duct anastomotic stricture.
2. Hepaticojejunal strictures
3. Post-ERCP pancreatitis prophylaxis (PEP)

## Secondary aims

* To determine the degradation time of the stents observed by abdominal radiograph (X-ray)
* To assess the requirement for second procedure to remove the stent
* To assess the rate of stricture resolution (clinical)
* To determine the need for repeat stenting for stricture resolution

# Study Design

## Study design

A prospective single arm study will be performed to assess the feasibility and safety of the novel bio-degradable stent (ARCHIMEDES) in management of patients with duct to duct anastomotic stricture, hepaticojejunal strictures and post ERCP pancreatitis prophylaxis.

## Centres

The study will be conducted at Endoscopy Unit, AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, a tertiary teaching hospital.

## Study groups and expected participant numbers

Patients will be enrolled into one of three study groups according to stenting indication:

Group 1: Duct to duct anastomotic stricture

Group 2: Hepaticojejunostomy stricture

Group 3: Requirement for a post ERCP pancreatitis prophylaxis

20 patients per group will be enrolled to a final number of 60 patients (as determined by the expected number of cases per annum).

## Duration of the study

Expected study duration including 1 year follow up – 3 years, data collection 1 July 2021— 1 July 2024.

# Inclusions and exclusion criteria

## Inclusion criteria

* Patients with clinical indication for ERCP with a duct to duct anastomotic stricture or hepaticojejunal stricture, or those who require pancreatic duct stent placement for post ERCP pancreatitis prophylaxis.

*Stricture definition: Narrowing of the bile duct less than 75% of the diameter in comparison to the unaltered bile duct or proximal dilatation on cross sectional imaging (CT cholangiogram or MRCP) OR the rise of cholestatic enzymes more than 2 times upper limit of normal (ALP and GGT)*

* Symptoms or signs: jaundice, cholangitis
* Age > 18 years old
* Able to give informed consent

## Exclusion criteria

* Contraindication for endoscopy
* Pregnancy
* Patients who had undergone any treatment to the stricture in the last 6 months
* Inability to pass a guidewire through stricture
* Malignant stricture
* Multiple concomitant bile duct strictures
* Stricture length > 8cm
* Anticoagulant therapy that cannot be discontinued prior to procedure

# Study procedures

## Investigational plan

Patients referred to the investigators who meet the selection criteria will be invited to participate in this study. Prior to the study commencement the patient will be reviewed either by the transplant team or an interventional gastroenterologist in order to confirm the indication for the procedure (for duct to duct anastomotic stricture and hepaticojejunal stricture).

The procedures will be conducted by consultant gastroenterologists and fellow who have qualifications in ERCP and accredited by the Conjoint Committee for the Recognition of Training in Gastrointestinal Endoscopy (CCRTGE).

Prior to study commencement, all endoscopists will receive a standardised 60-minute training module reviewing the study protocol, methods and data recording. The study protocol will be available at the study centre.

Eligible patients will be approached and have the study explained to them by an investigator and be provided with a Patient Information Sheet. If an outpatient, they will be provided with at least 1 week to consider participation in the study. Inpatients will be given up to 24 hours to consider participation. Their surgery will proceed as planned regardless of their study participation. The consenting process will be carried out by a medical officer who is a researcher and independent from the attending medical team.

Post ERCP and biliary stent placement (groups 1 and 2), patients will undergo liver function tests at

* week 1
* 1 month
* 3 months
* 6 months
* 9 months
* 12 months

Abdominal X-ray will be performed to ensure complete stent degradation at:

* 1 month
* 3 months
* 6 months

Table 1 Showing study plan and timeline

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Interventions | Enrolment Visit | Procedure day | Follow up week 1 | Follow up week 2 | Follow up 1 month | Follow up 3 months | Follow up 6 months  | Follow up 9 months  | Follow up 12 months  |
| Inclusion / Exclusion criteria | ✓ |  |  |  |  |  |  |  |  |
| Participant Consent |  | ✓ |  |  |  |  |  |  |  |
| Procedure |  | ✓ |  |  |  |  |  |  |  |
| Blood liver function test |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| X ray |  |  |  |  | ✓ | ✓ | ✓ |  |  |

*For patients in group 3, follow up at 1 week with a phone call for clinical assessment about post procedure pain, admission for pancreatitis. Second follow up at 4 weeks with abdominal X-ray to ensure complete stent degradation.*

## Biodegradable stents (ARCHIMEDES)

Biodegradable biliary and pancreatic stents (ARCHIMEDES stent) are intended to be used to drain obstructed biliary or pancreatic ducts. The patented helical design of the stent allows for bile to flow on the outer extremity of the device while supporting the opening of the lumen. It has the following potential advantages:

* Three degradation profiles (fast, medium and slow) to address all biliary and pancreatic drainage indications
* Potential to reduces cost, morbidity and complication rates by eliminating subsequent stent removal procedure
* Proximal and distal flaps to help minimize migration
* Anatomical shape to enhance positioning
* Tapered tip to facilitate smooth cannulation
* Helical bile channels to allow for anatomical bile flow

They have different degradation profiles, , this study will be using stents with the fast biodegradation rate (12 days, ARTG ID 335506) and the slow biodegradation rate (11 weeks, ARTG ID 335504). Stent degradation of synthetic biodegradable polyester polymers occurs via hydrolysis. The degradation time is the minimal strength retention defined by the presence of at least 10% of an initial strength parameter. This evaluation was conducted in vitro by the manufacturer in a simulated degradation model.

Fluoroscopic visualization is facilitated by incorporation of barium sulphate in the stent material, while stent migration is minimized by proximal and distal flaps. Stents are available in 3 outer diameters: 2 mm (6Fr), 2.6 mm (8Fr) and 3.4 mm (10Fr) and in lengths ranging from 40 mm up to 125 mm.

For patients in group 1 and 2, slow degrading stents will be used. For patients in group 3, fast degrading stents will be used.

## Endoscopic procedure

All endoscopic procedures will be performed with propofol-based deep sedation or general anaesthetic, with a consultant anaesthetist. A standard duodenoscope (Olympus, Japan) will be used for all procedures. Rectal indomethacin will be administered in patients where it is considered to be necessary (to prevent post procedure pancreatitis).

Group 1

Biliary cannulation will be performed with standard short guidewire and sphincterotome. If necessary, a sphincterotomy will be conducted. Prior to placement the biodegradable stent will be pre-activated by immersion in sterile saline for one minute. Insertion is performed over a guidewire through the working channel of the duodenoscope using a standard ERCP catheter. Insertion will be done under radiologic visualization. A cholangiogram will be obtained.

In patients with duct-to-duct biliary reconstruction, the stricture will be dilated with the aim to place stents to total diameter of 16Fr – 20Fr (2 x 8Fr stents or 10Fr). The stent size and number chosen will be determined based on findings at cholangiogram during ERCP. If the patient has undergone liver transplant within 8 weeks of ERCP, dilatation will not be performed and only a single stent will be placed.

Group 2

In patients with hepaticojejunostomies, double balloon ERCPs will be performed with a double balloon enteroscope (Fujinon, Japan) and dilations of the anastomosis will be carried out with the aim of placing stents up to 16 - 20Fr in diameter (again the size and number will be chosen based on findings at cholangiogram). If the patient has undergone liver transplant within 8 weeks of ERCP, dilatation will not be performed and only a single stent will be placed.

Group 3

In patients undergoing ERCP where a pancreatic stent is required for PEP prophylaxis (as per endoscopist discretion), a 6Fr pancreatic stent will be deployed.

## Complications

The main complications of the ERCP are pancreatitis, infection and bleeding [3]. In comparison to the normally used plastic and metal stent there is not a higher risk expected with the biodegradable stents.

# Study endpoints and definitions

## Primary outcome measurements

* Ability to deploy the stent in the desired position.

## Secondary outcome measurements

* Lack of stent degradation will be assessed in fast and slow degradation groups
	+ Groups 1 and 2 (slow degradation group); Lack of complete stent degradation monitored with X Ray at days 30, 90, 180 after treatment. Partial degradation is defined as a reduction in stent length and integrity between 75% and 25%; complete degradation of the stent is defined as <25% of stent length or stent’s fragments visible at radiograph.
	+ Group 3 (fast degradation group): Lack of complete stent degradation will be monitored with X ray at week 2 in these subjects with same definitions for partial and complete degradation as above
* Patient undergoes repeat ERCP for stent removal
* Stricture resolution, defined as reduction of at least 50% of the initial serum bilirubin level or cholestatic enzymes at day 14 post stenting for benign biliary strictures and persistent decline of cholestasis at 3 month follow up
* Clinical failure of stricture resolution defined as; need for repeat ERCP and stenting within 6 months of primary ERCP or clinically indicated by cholestasis (ALP/GGT > 2x upper limit of normal or bilirubin >20)

Each participant will be assigned a study code that will be recorded on the Patient code sheet. This code will be used for the case report form. Case report forms will be used to record previous medical history relevant and capsule and bidirectional endoscopies procedures.

# Data analysis

Data will be analysed descriptively. Baseline characteristics of the patient population, BE characteristics, technical details, and procedure outcomes will be summarised as a mean (SD) or median (with interquartile range [IQR] and range) for continuous data, and as frequencies and proportions for categorical data. All statistical analysis will be performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

# Ethical considerations

## Ethical Approval

The Principal Investigator and site Investigators are responsible for submitting this protocol and all supporting documents to the relevant Human Research Ethics Committee (HREC). HREC approval followed by Research Governance Office authorisation will be obtained before the study can be commenced.

These Investigators are also responsible for overseeing the research project and ensuring that protocol is maintained. Any adverse events or changes to protocol will be reported to the Ethics Committee. Participants undergoing the study will have received information on the study and have signed an informed consent form.

## Informed Consent

Patients will undergo a consultation with study Doctors to discuss all aspects of involvement in the study. Patients will be given information and if the consultant feels that the patient has the capacity to provide their own consent a patient consent form will be provided to them. The consenting process will be carried out by a medical officer (endoscopy fellow) who is a researcher and independent from the attending medical team. If the patient meets the inclusion and exclusion criteria for the study, they will be consented for participation by the endoscopy fellow. If an outpatient, they will be provided with at least 1 week to consider participation in the study. Inpatients will be given up to 24 hours to consider participation. Their surgery will proceed as planned regardless of their study participation.

All patients will be provided an opportunity to discuss the study, and its potential benefits and risks. It will be explained clearly to all patients that participation in the study is voluntary and that they are free to withdraw consent at any time during the study. Once all questions have been addressed, if willing to consent to the study, the patient will be asked to sign the consent form.

Flowchart 1. Outpatients

Flowchart 2. Inpatients

## Confidentiality

To protect patient’s confidentiality, the subjects name will not appear on any documentation; rather each patient will be given a specific code that will be used. The patients code will only be known to the study Investigators in the case of the need for identification and to provide adequate clinical care.

## Adverse Event Reporting

Any adverse events experiences by a patient will be discussed with a study Doctor and documented. Appropriate treatment and follow-up will be given to the patient. The study Investigators will consider if this event is related to the study procedure. Any adverse events will be reported to the Ethics Committee.

## Patient Safety

The endoscopic procedures will be performed to the same clinical standard of any normal procedure. They will be performed in the Endoscopy Unit at Royal Prince Alfred Hospital with qualified Doctors and nurses. Great care will be taken to reduce all adverse events and complications due to the procedure. Furthermore, patients will have the contact details for the Endoscopy unit and study investigators in case any symptoms or concerns arise once they have been discharged. All patients will be advised to present to the Royal Prince Alfred Hospital emergency department if new or worsening symptoms arise (abdominal pain, fevers, rigors, chills, nausea, vomiting or any symptom of concern).

Patient’s data will be confidential and no data collection forms will include subject names, instead a specific code will be used. Publications and research reports will be de-identified.

## Data safety and monitoring board (DSMB)

Dr Charbel Sandroussi and Dr David Yeo have been nominated as the members of the study DSMB. The study data will be reviewed by the DSMB after the initial 5 patients and monthly thereafter.

# Study Termination

Any patient enrolled in the study is able to withdraw at any point in time, effective immediately. Investigators are also able to withdraw patients from the trial if they see it as medically necessary. Any withdrawals from the study will be documented with the reasons outlined.

# Information security

## Data Flow

After enrollment in the study, any relevant medical information will be collected from the patient and hospital records as detailed in the case report form. Each patient will be assigned a unique study code that will be recorded on the patient code sheet along with the identifiable information. Only coded information will be recorded on the CRF. In accordance with GCP, data will be updated as part of day to day management of the study. Information and documentation will be accessible, clearly ordered and comprehensible. The paper copies of the Form will be confidential and securely stored within the locked filing cabinet in the doctor’s office, Endoscopy unit, AW Morrow Gastroenterology and Liver Centre. The data will be imported into the REDCap data management system; a secure, encrypted database that stores and regularly backs up data within the SLHD ICT services environment. Only personnel involved in the study will be allowed access to the data.

Endoscopy reports containing images are part of the patient’s medical records and will be stored on the hospital’s electronic medical record (as is standard practice).

Once participants have completed the study, investigators will review the data for any discrepancies requiring further follow-up. Data will be de-identified for research purposes.

## Data Destruction

At the completion of the study, all data will remain stored for 5 years after publication after which all files can be destroyed electronically. Any paper records will be shredded and destroyed after 5 years after publication.

## Terminations of Data Access

In the event that the Principal Researcher/Investigator ceases to be engaged at the current organisation, an Associate Investigator involved in the study will then become the Principal Investigator. No data will be moved from the location outlined in this protocol.

# References

1. Anderloni A, Fugazza A, Maroni L, et al. New biliary and pancreatic biodegradable stent placement: a single-center, prospective, pilot study (with video). Gastrointest Endosc 2020;92:405-411.

2. Siiki A, Vaalavuo Y, Antila A, et al. Biodegradable biliary stents preferable to plastic stent therapy in post-cholecystectomy bile leak and avoid second endoscopy. Scand J Gastroenterol 2018;53:1376-1380.

3. Siiki A, Rinta-Kiikka I, Sand J, et al. Biodegradable biliary stent in the endoscopic treatment of cystic duct leak after cholecystectomy: the first case report and review of literature. J Laparoendosc Adv Surg Tech A 2015;25:419-22.