Colchicine for patients with aortic stenosis undergoing transcatheter aortic valve replacement (Co-STAR): a randomized-controlled trial

Clinical Study Protocol

Study Type:	Clinical trial on investigational medicinal product
Study Categorisation:	Risk category C
Study Registration:	ClinicalTrials.gov ID: NCT04870424
Study Identifier:	Co-STAR
Sponsor:	Insel Gruppe AG, Inselspital Bern, Universitätsklinik für Kardiologie
Sponsor-Investigator/ PI Inselspital:	Prof. Dr. med. Thomas Pilgrim Stv. Chefarzt Kardiologie Medizinbereich Herz/Gefäss Inselspital Bern Freiburgstrasse 10 3010 Bern (Switzerland) Phone: +41 31 632 08 27 Mail: thomas.pilgrim@insel.ch
Investigational Product:	Colchicine
Protocol Version and Date:	Version 4, 22.07.2021

Signature Pages

Signature page Sponsor-Investigator

Study number	ClinicalTrials.gov ID: NCT04870424
Study Title	Colchicine for patients with aortic stenosis undergoing transcatheter aortic valve replacement (Co-STAR).

The Sponsor-Investigator has approved the protocol version 4 (dated 22.07.2021) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator: Prof. Dr. med. Thomas Pilgrim

Place/Date	Signature

Signature Pages

Signature page Trial Statistician

Study number	ClinicalTrials.gov ID: NCT04870424
Study Title	Colchicine for patients with aortic stenosis undergoing transcatheter aortic valve replacement (Co-STAR).

The trial statistician has approved the protocol version 4 (dated 22.07.2021) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Trial Statistician: PD Dr. Dik Heg

Place/Date	Signature

Signature Pages

Signature page steering committee members

Study number	ClinicalTrials.gov ID: NCT04870424
Study Title	Colchicine for patients with aortic stenosis undergoing transcatheter aortic valve replacement (Co-STAR).

The co investigators have approved the protocol version 4 (dated 22.07.2021), and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Local-Principal Investigator: Prof. Dr. med. Thomas Pilgrim

Place/Date	Signature

Co- Investigator: Dr. med. Christoph Ryffel

Place/Date	Signature

Co- Investigator: Dr. med. Jonas Lanz

Place/Date	Signature

Table of Contents

STUDY SYNOPSIS **8**
ABBREVIATIONS **13**
STUDY SCHEDULE **15**
1. STUDY ADMINISTRATIVE STRUCTURE **16**
1.1 Sponsor/Sponsor-Investigator 16
1.2 Principal Investigator/Co-Principal Investigators Inselspital Bern 16
1.3 Statistician ("Biostatistician") 17
1.4 Monitoring institution 17
1.5 Steering Committee 17
1.6 Data Safety Monitoring Committee 17
1.7 Any other relevant Committee, Person, Organisation, Institution 17
2. ETHICAL AND REGULATORY ASPECTS **18**
2.1 Study registration 18
2.2 Categorisation of study 18
2.3 Approval from and reporting to Competent Ethics Committee and Competent Authorities (CA) 18
2.4 Ethical Conduct of the Study 19
2.5 Declaration of interest 19
2.6 Patient Information and Informed Consent 19
2.7 Participant privacy and confidentiality 19
2.8 Early termination of the study 19
2.9 Significant changes 19
3. BACKGROUND AND RATIONALE **21**
3.1 Background and Rationale 21
3.2 Investigational Product and Indication 21
3.3 Preclinical Evidence 21
3.4 Clinical Evidence to Date 22
3.5 Dose Rationale: Rationale for the intended purpose in study (pre-market MD) 22
3.6 Explanation for choice of comparator (or placebo) 22
3.7 Risks / Benefits 22
3.7.1 Main Side Effects of Colchicin: 23
3.7.2 Benefits 23
3.8 Justification of choice of study population 23
4. STUDY OBJECTIVES **24**
4.1 Overall Objective 24
4.2 Primary Objective 24
4.3 Secondary Objectives 24
4.4 Safety Objectives 24
5. STUDY OUTCOMES **25**
5.1 Primary Outcome 25
5.2 Secondary Outcomes 25
5.3 Safety Outcomes 25
6. STUDY DESIGN **26**
6.1 General study design and justification of design 26
6.2 Methods of minimising bias 26
6.2.1 Randomisation 26

6.2.2 Blinding procedures 26
6.2.3 Other methods of minimising bias 26
6.3 Unblinding Procedures (Code break) 26
7. STUDY POPULATION 27
7.1 Eligibility criteria 27
7.2 Recruitment and screening 27
7.3 Assignment to study groups 27
7.4 Criteria for withdrawal / discontinuation of participants 28
8. STUDY INTERVENTION 29
8.1 Identity of Investigational Products 29
8.1.1 Experimental Intervention (treatment) 29
8.1.2 Control Intervention (standard/routine/comparator treatment) 29
8.1.3 Packaging, Labelling and Supply 29
8.1.4 Storage Conditions 29
8.2 Administration of experimental and control interventions 29
8.2.1 Experimental Intervention 29
8.2.2 Control Intervention 29
8.3 Compliance with study intervention 29
8.4 Data Collection and Follow-up for withdrawn participants 29
8.5 Concomitant Interventions (treatments) 30
8.6 Study Drug Accountability 30
8.7 Return or Destruction of Study Drug 30
9. STUDY ASSESSMENTS 31
9.1 Study flow chart(s) / table of study procedures and assessments 31
9.2 Assessments of outcomes 32
9.2.1 Assessment of primary outcome 32
9.2.2 Assessment of secondary outcomes 32
9.2.3 Assessment of other outcomes of interest 32
9.2.4 Assessment of safety outcomes 32
9.2.5 Assessments in participants who prematurely stop the study 33
9.3 Procedures at each visit 33
9.3.1 Screening visit, Day -30 to -1. 33
9.3.2 Visit 1 (during in-hospital stay), Day -1 33
9.3.3 Visit 2 (during in-hospital stay), Day 2 until discharge 33
9.3.4 After discharge until day 30 33
9.3.5 Visit 3, Day 30-37 33
9.3.6 Visit 4, 1 year (+ 21 days) 34
10. SAFETY 34
10.1 Drug studies 34
10.1.1 Definition and assessment of (serious) adverse events and other safety related events 34
10.1.2 Reporting of serious adverse events (SAE) and other safety related events 35
10.1.3 Follow up of (Serious) Adverse Events 35
11. STATISTICAL METHODS 36
11.1 Hypothesis 36
11.2 Determination of Sample Size 36
11.3 Statistical criteria of termination of trial 36

11.4 Planned Analyses 37
11.4.1 Datasets to be analysed, analysis populations 37
11.4.2 Primary Analysis 37
11.4.3 Secondary Analyses 37
11.4.4 Interim analyses 37
11.4.5 Safety analysis 37
11.4.6 Deviation(s) from the original statistical plan 37
11.5 Handling of missing data and drop-outs 37
12. QUALITY ASSURANCE AND CONTROL 38
12.1 Data handling and record keeping / archiving 38
12.1.1 Case Report Forms 38
12.1.2 Specification of source documents 38
12.1.3 Record keeping / archiving 38
12.2 Data management 38
12.2.1 Data Management System 38
12.2.2 Data security, access and back-up 39
12.2.3 Archiving 39
12.2.4 Electronic and central data validation 39
12.3 Monitoring 39
12.4 Audits and Inspections 39
12.5 Confidentiality, Data Protection 39
13. PUBLICATION AND DISSEMINATION POLICY 40
14. FUNDING AND SUPPORT 41
14.1 Funding 41
15. INSURANCE 41
16. REFERENCES 42
17. APPENDICES 44

STUDY SYNOPSIS

Sponsor / Sponsor-Investigator and PI Inselspital Bern	Insel Gruppe AG, Inselspital Bern, Universitätsklinik für Kardiologie / Prof. Dr. med. Thomas Pilgrim
Study Title:	Colchicine for patients with aortic stenosis undergoing transcatheter aortic valve replacement (Co-STAR): a randomized-controlled trial
Short Title / Study ID:	Co-STAR
Protocol Version and Date:	Version 4, 22.07.2021
Trial registration:	ClinicalTrials.gov ID: NCT04870424
Study category and Rationale	HRA/ClinO/Clinical Trial with Medicinal Product Risk category C, since colchicine is not authorised in Switzerland.
Clinical Phase:	Phase 3 study
Background and Rationale:	Transcatheter aortic valve implantation (TAVI) is a well-established alternative to surgical aortic valve replacement (SAVR) for the treatment of patients with symptomatic severe aortic stenosis (AS). While peri-procedural complications such as stroke, vascular complications and bleeding have substantially declined with the refinement of transcatheter valves and increasing experience, new-onset atrial fibrillation (NOAF) and atrioventricular conduction disturbances continue to occur in almost half of all patients and represent an ongoing challenge for the expansion of TAVI towards younger patients at low surgical risk. Colchicine has proven safe and effective in the prevention of atrial fibrillation after cardiac surgery. Injury to the atrioventricular (AV) node and left bundle branches due to a transient inflammation and tissue edema is an important mechanism involved in the development of conduction disturbances after TAVI. The anti-inflammatory effects of colchicine may mitigate the occurrence of atrioventricular conduction disturbances and thus the need for the implantation of a permanent pacemaker post TAVI.
Objective:	The objective of the present study is to investigate the efficacy of colchicine for the prevention of NOAF and conduction disturbances requiring the implantation of a permanent pacemaker in patients undergoing TAVI.

Outcomes:	Primary endpoint: Composite of NOAF or the occurrence of conduction disturbances requiring the implantation of a permanent pacemaker in the first 30 days post TAVI in patients treated with colchicine or placebo. <u>Secondary endpoints:</u> - The incidence of NOAF (at 30 days, 1 year). - The incidence of conduction disturbances requiring the implantation of a permanent pacemaker (at 30 days, 1 year). - The incidence and predictors of conductance disturbances: new or worsened first-degree atrioventricular (AV) block, second-degree AV block (Mobitz I or Mobitz II), high-grade atrioventricular block, third-degree AV block, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block, intraventricular conduction delay (at 30 days, 1 year). - The incidence of new arrhythmias resulting in hemodynamic instability or requiring therapy (defined as electrical/medical cardioversion or initiation of a new medication e.g. oral anticoagulation, rhythm, or rate controlling therapy) (at 30 days, 1 year). - The difference in inflammatory marker levels in patients treated with colchicine or placebo at day 1 post TAVI. - The proportion of patients with at least one prosthetic leaflet with > 50% motion reduction or with at least one prosthetic leaflet with thickening (at 30 days). - The proportion of prosthetic leaflets with > 50% motion reduction or leaflet thickening (at 30 days). - The incidences of major clinical adverse events such as all-cause mortality, stroke, transient ischemic attack, bleeding event, kidney injury, systemic embolism, myocardial infarction, infections, clinical valve thrombosis at 30 days and 1 year post-TAVI in patients treated with colchicine or placebo. -
Study design:	Investigator-initiated, randomized, double-blind, placebo-controlled, monocentric clinical study.

Inclusion / Exclusion criteria:	Inclusion criteria: 1. Age ≥ 65 years 2. Symptomatic severe aortic stenosis defined by an aortic valve area (AVA) ≤1.0 cm^2 or an AVA indexed to body surface area <0.6cm^2/m^2 3. Selected to undergo transfemoral TAVI based on heart team decision Exclusion criteria: 1. Life expectancy <1 year irrespective of valvular heart disease 2. Kidney disease with a creatinine clearance ≤30 ml/min 3. Known severe liver disease 4. Known neuromuscular disease 5. Clinically significant anaemia with haemoglobin <80g/L 6. Known inflammatory bowel disease or chronic diarrhea 7. Known ongoing bacterial infection 8. Known galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 9. Current treatment with colchicine, steroids or biologicals for any indication 10. Concomitant intake of Cyclosporine, Amiodaron, Clarithromycin, Erythromycin, Omeprazol, Verapamil or other strong inhibitors of CYP3A4 or P-Glycoprotein 11. Concomitant intake of Carbamazepin, Phenobarbital, Phenytoin, Rifampicin or other strong inductors of CYP3A4 and P-Glycoprotein 12. Permanent pacemaker or implantable cardioverter defibrillator 13. History of atrial fibrillation 14. Absence of sinus rhythm on hospital admission 15. Planned non-cardiac surgery within 30 days 16. Known intolerance to colchicine 17. Inability to provide informed consent 18. Known or suspected non-compliance, drug or alcohol abuse 19. Participation in another clinical trial with an active intervention 20. Any other planned cardiac intervention performed in the 7 days before TAVI, concomitantly with TAVI or in the 30 days after TAVI except for percutaneous coronary interventions.

Measurements and procedures:	Patients referred for treatment of symptomatic severe aortic stenosis and selected to undergo TAVI based on heart team decision will be screened for eligibility. If eligible, patients will be allocated in a 1:1 ratio to either the treatment (colchicine) or the control arm (placebo) by means of randomly permuted block randomization stratified on presence or absence of right bundle branch block. Study medications will be started one day before TAVI and administered for the duration of 12 days post-TAVI. Inflammatory laboratory markers will be measured on post-procedural day 1, blood will be drawn at the time of routine blood withdrawal in the context of TAVI. Patients will be continuously tele-monitored for rhythm disorders up to discharge. At discharge, a 7-day long-term rhythm monitoring will be conducted. At 30 days a clinical follow up will take place, which will include: - clinical endpoint ascertainment - assessment of long-term rhythm monitoring to capture clinically silent NOAF, other arrhythmias or AV-conductance disturbances - 12-lead electrocardiogram to assess for conductance disturbances - Cardiac computed tomographic angiography (CCTA) to assess HALT and leaflet-motion abnormalities - ascertainment of current medical treatment - capture of potential drug-related adverse effects - monitoring of the patient's blood count, hepatic and renal function At 1 year a clinical follow up will take place, which will include: - standardized telephone interview for clinical endpoint ascertainment - 12-lead electrocardiogram to assess for conductance disturbances (performed on-site or by referring physician)
Study Product (investigational medicinal product) / Intervention:	Colchicine is an alkaloid interfering with the intracellular assembly of the microtubules of the cytoskeleton of cells; by its anti-mitotic effect it interferes with downstream cellular functions of leucocytes, in particular neutrophils and monocytes, which explains its anti-inflammatory effects. Colchicine is a well-known agent and in many countries approved to e.g. treat acute gout flares and familial Mediterranean fever. Colchicine will be administered in a loading dosage of 1mg single dose per os the day before TAVI and 1mg single dose at the day of procedure. Thereafter, colchicine 0.5mg will be administered once daily per os up to post-procedural day 12.
Control Intervention:	Placebo will be administered corresponding to IMP once daily per os the day before TAVI and once at the day of procedure. Thereafter, placebo will be administered once daily per os up to post-procedural day 12.
Number of Participants with Rationale:	Based on an anticipated incidence proportion of 42% for the primary composite endpoint at 30 days in the control arm and an expected relative risk reduction of 45%, 100 patients are required per study group to show superiority of the intervention with a power of 80% at a two-tailed significance level of $\alpha = 0.05$ and a low attrition and cross-over rate.
Study Duration:	Preparatory phase: 3 months Recruitment period: 36 months Follow-up per patient: 12 month Duration of the entire trial (preparatory phase, recruitment, follow-up, analysis): 54 months

Study Schedule:	First participant enrolled: July 1, 2021 Last participant enrolled: June 30, 2024 Last 30-day follow-up (primary endpoint): July 31, 2024. Last 12-month follow-up: June 30, 2025 Study completion: September 30, 2025
Investigators:	Sponsor Investigator and PI Inselspital Bern: Prof. Dr. med. Thomas Pilgrim Stv. Chefarzt Kardiologie Medizinbereich Herz/Gefäss Inselspital Bern Freiburgstrasse 10 3010 Bern, Switzerland Phone: +41 31 632 08 27 E-mail: thomas.pilgrim@insel.ch Co- Investigator: Dr. med. Christoph Ryffel Structural Heart Disease Fellow Medizinbereich Herz/Gefäss Inselspital Bern Freiburgstrasse 10 3010 Bern, Switzerland Phone: +41 31 632 21 11 E-mail: christoph.ryffel@insel.ch Co- Investigator: Dr. med. Jonas Lanz Oberarzt Kardiologie Medizinbereich Herz/Gefäss Inselspital Bern Freiburgstrasse 10 3010 Bern, Switzerland Phone: +41 31 632 21 11 E-mail: jonas.lanz@insel.ch
Study Centres:	Inselspital, Bern University Hospital, Bern, Switzerland
Statistical Considerations:	The primary composite endpoint at 30 days in the two treatment arms will be compared by means of the risk difference. The superiority assumption will be tested at a two-sided significance level with a type I error rate (α) = 0.05. Primary endpoint analysis will be conducted according to the intention-to-treat (ITT) principle. Sensitivity analyses will be performed in the as-treated cohort (AT), whereby patients will be analysed according to whether they have been taking the study medication for the first 7 days after initiation or not. Secondary analyses will evaluate between group differences in relation to inflammatory marker levels at post-procedural day 1, hypoattenuated leaflet thickening and restricted leaflet motion based on CCTA at 30 days and individual clinical endpoints, potential adverse effects, conductance disturbances and arrhythmias at 30 days and 1 year.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 as applicable as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
AF	Atrial fibrillation
AS	Aortic Stenosis
AV	Atrioventricular
AVA	Aortic Valve Area
BASEC	Business Administration System for Ethical Committees
BID	Bis In Die
CA	Competent Authority (e.g. Swissmedic)
CDMS	Clinical Data Management System
CEC	Competent Ethics Committee
CRF	Case Report Form
CRP	C-Reactive Protein
CCTA	Cardiac computed tomography angiography
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DSMB	Data and Safety Monitoring Board
DSUR	Development safety update report
FUP	Follow-Up Procedure
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International conference on harmonization
Ho	Null hypothesis
HALT	Hypo-Attenuating Leaflet Thickening
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ILR	Implantable Loop Recorder
ISO	International Organisation for Standardisation
ITT	Intention to treat
MD	Medical Device
NOAF	New Onset Atrial Fibrillation
PI	Principal Investigator
RCT	Randomized Controlled Trial
RR	Risk Ratio
SDV	Source Data Verification

SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SAVR	Surgical Aortic Valve Replacement
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAVI	Transcatheter Aortic Valve Implantation
TTE	Transthoracic Echocardiogram
TMF	Trial Master File

STUDY SCHEDULE

Study Periods	Screening	Intervention Period		Follow-up	
Visit	S	1	2	3	4*
Time (day (d) or month (mo))	-30 to -1d	-1d	post-TAVI until discharge	30 to 37d	12mo (+21d)
Patient Information and Informed Consent	x[1]				
Demographics	x				
Medical History	x	x	x	x	x
In-/Exclusion Criteria	x[1]				
Physical Examination	x	x			
Vital Signs	x	x	x	x	
Laboratory Tests**	x	x	x[1]	x[1]	
Randomisation	x[1]				
12-lead ECG***	x	x	x	x	x
TTE	X[2]		x	x	
CCTA	x			x[1]	
Administer Study Medication****		x[1]	x[1]		
Rhythm Monitoring*****			x[1]		
Primary Outcome assessment				x[1]	
Secondary Outcome assessment				x[1]	x[1]
Adverse Events per section 5.3		x[1]	x[1]	x[1]	x[1]
Serious Adverse Events		x[1]	x[1]	x[1]	x[1]
Phone Call					x[1]
Scheduling next follow-up			x[1]		
Adherence to IMP				x	
Collection of Routine data [+]	x	x	x	x	x

* Visit or phone call: available routine data will be collected (e.g. TTE) as per Swiss TAVI registry. FUP, if possibly, will be combined with the FUP for the Swiss TAVI registry.

** Routine tests at day before TAVI: CK, hs-Troponin T, NT-pro BNP, haemoglobin, haematocrit, leukocytes, thrombocytes, CRP, glucose, HbA1c, creatinine, lipids (including cholesterol, HDL, LDL, triglycerides), ALAT, ASAT, Gamma-GT, albumin, INR, bilirubin, TSH.

Routine tests day 1 post-TAVI: haemoglobin, haematocrit, leukocytes, thrombocytes, glucose, creatinine

In addition:

- Monitoring of blood count, hepatic and renal function every day until hospital discharge and at 30 day visit: Haemoglobin, haematocrit, thrombocytes, leucocytes, creatinine, ALAT, ASAT, Gamma-GT, Bilirubin, INR
- Study specific inflammatory markers at day 1 post-TAVI: CRP, high-sensitivity CRP , and not mandatory: IL-6, IL-8, TNF-alpha, IL-1β (results will be stored separately to avoid potential unblinding of study personnel)

*** At 12 months performed on-site or by referring physician.

**** loading dosage of 1mg colchicine single dose or placebo per os the day pre-TAVI and 1mg single dose or placebo at the day of procedure. Afterwards, 0.5mg or placebo once daily per os up to post-procedural day 12. First IMP administration should whenever possible take place 20-28 hours before TAVI but not less than 12 hours before second IMP administration and following TAVI.

***** Telemonitoring until discharge. At discharge, a 7-day long-term rhythm monitoring will be conducted.

[1] Study specific intervention

[2] In Addition: Optional Transesophageal echocardiography (only if available as routine data).

[+] Routine Data will be collected for the study, in particular data on routine CT and cardiac catheterization before TAVI Intervention and data of Intervention.

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor/Sponsor-Investigator

Insel Gruppe AG, Inselspital Bern, Universitätsklinik für Kardiologie/

Prof. Dr. med. Thomas Pilgrim

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1.2 Principal Investigator/Co- Investigators Inselspital Bern

Prof. Dr. med. Thomas Pilgrim

Stv. Chefarzt Kardiologie

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Dr. med. Jonas Lanz

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1.3 Statistician ("Biostatistician")

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1.4 Monitoring institution

Independent on-site Monitoring Visits will be performed according the Monitoring Plan by:

Clinical Trial Unit Bern

Mittelstrasse 43

CH-3012 Bern

1.5 Steering Committee

The steering committee is responsible of the overall management of the study. The steering committee members are Prof. T. Pilgrim, Dr. Jonas Lanz and Dr. Christoph Ryffel.

1.6 Data Safety Monitoring Committee

Members of the Data Safety Monitoring Board (DSMB) are not affiliated with the site enrolling patients into the trial, are not participating in the trial, and will declare any conflicts of interest should they arise. The composition, guiding policies, and operating procedures governing the DSMB are described in a separate charter.

The Data Safety Monitoring Board will evaluate the safety of the trial and the trial intervention after in regular manner as defined per DSMB charter.

1.7. Clinical Event Committee

The events are adjudicated by the clinical event committee comprising qualified physicians who are not investigators in the trial. The clinical event committee is responsible for adjudicating all potential primary endpoint events as well as events as defined per clinical event committee charter. The members of the Clinical Event Committee will be blinded to the patient's treatment allocation.

1.7 Any other relevant Committee, Person, Organisation, Institution

Insel Gruppe AG

Institut für Spitalpharmazie

Freiburgstrasse

3010 Bern

Main tasks (list not exhaustive): Import, Capsulation and labelling of IMP/Placebo.

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol, the proposed patient information and consent form as well as other required study-specific documents will be submitted to the local Competent Ethics Committee (CEC) and competent regulatory authority (Swissmedic) in agreement with local legal requirements, for formal approval. Any amendment to the protocol must as well be approved (if legally required) by these institutions.

The decision of the CEC and Swissmedic concerning the conduct of the study will be made in writing to the Sponsor/Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

ClinicalTrials.gov ID: NCT04870424. The study will be registered as well in the Swiss National Clinical trial Portal (SNCTP).

2.2 Categorisation of study

HRA/ClinO/ Clinical Trial with Medicinal Product Risk category C, since colchicine is not authorised in Switzerland.

2.3 Approval from and reporting to Competent Ethics Committee (CEC) and Competent Authorities (CA)

The sponsor ensures that approval from an appropriately constituted Competent Ethics Committee (CEC) and competent authority is sought for the clinical study.

Reporting

The notification and reporting is defined by HRA/ClinO Section 5. Specifically:

Notification of safety and protective measures:

If immediate safety and protective measures have to be taken during the conduct of a clinical trial, the investigator shall notify the CEC/CA of these measures, and of the circumstances necessitating them, within 7 days.

Notification and reporting upon completion, discontinuation or interruption of a clinical trial

The sponsor shall notify the CEC/CA of the completion of the clinical trial in Switzerland within 90 days. Completion of a clinical trial is marked by the last participant's final follow-up visit.

The sponsor shall notify the CEC/CA of the discontinuation or interruption of the clinical trial within 15 days. In the notification, the reasons for the discontinuation or interruption shall be stated.

The sponsor shall submit a final report to the CEC/CA within a year after completion or discontinuation of the clinical trial, unless a longer period is specified in the protocol.

Death:

The sponsor shall notify the responsible CEC of a fatal serious adverse event occurring at a trial site in Switzerland within 7 days.

Suspected unexpected serious adverse reaction (SUSAR):

The Sponsor shall notify the responsible CEC/CA of a fatal suspected unexpected serious adverse reaction within 7 days, and of any other suspected unexpected serious adverse reaction within 15 days.

Annual Safety Reports:

Once a year, the investigator shall present to the CEC/CA a list of all serious adverse events and SUSARs (ClinO Art 40, 41) and shall submit a report on their severity and causal relationship to the medicinal product, and on the safety of participants (annual safety report, ASR).

2.4 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki,(1) the guidelines of Good Clinical Practice (GCP) issued by ICH(2) and the Swiss Law and Swiss regulatory authority's requirements.

2.5 Declaration of interest

No conflict of interests.

2.6 Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Ample time will be given to consider study participation.

The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.7 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.8 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of the clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.9 Significant changes

Significant changes to an authorised clinical trial must be reported to CEC/CA according HRA/ClinO Art 29, Art 34.

The Sponsor-Investigator must approve changes to the authorized clinical trial and seek approval before implementation from:

Significant changes approved by ethics committee (CEC):

Significant changes to an authorised clinical trial must be authorised by the ethics committee before being implemented. Exempt from this requirement are measures which have to be taken immediately in order to protect the participants. Other changes must be notified to the ethics committee in the annual safety report.

The following are considered to be significant changes:

a. changes affecting the participants' safety and health, or their rights and obligations;

b. changes to the protocol, and in particular changes based on new scientific knowledge which concern the trial design, the method of investigation, the endpoints or the form of statistical analysis;

c. a change of trial site, or conducting the clinical trial at an additional site; or

d. a change of sponsor, coordinating investigator or investigator responsible at a trial site.

Note: Other changes which affect the documents submitted to the Agency (CA) must be notified to the Agency as quickly as possible.

Significant changes with approval by Competent Authorities (CA):

Significant changes to an authorised clinical trial must be authorised by the Agency (CA) before being implemented. Exempt from this requirement are measures which have to be taken immediately in order to protect the participants.

The following are considered to be significant changes:

- changes to the therapeutic product, or to its administration or use;

- changes based on new preclinical or clinical data which may affect product safety; or

- changes concerning the production of the therapeutic product which may affect product safety.

Note: Other changes which affect the documents submitted to the Agency must be notified to the Agency as quickly as possible.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Transcatheter aortic valve implantation (TAVI) is a well-established alternative to surgical aortic valve replacement (SAVR) for the treatment of patients with symptomatic severe aortic stenosis (AS).(9) While peri-procedural complications such as stroke, vascular complications and bleeding have substantially declined with the refinement of transcatheter valves and increasing experience, new-onset atrial fibrillation (NOAF) or atrioventricular conduction disturbances continue to occur in almost half of all patients and represent an ongoing challenge for the expansion of TAVI towards younger patients at low surgical risk.

Atrial fibrillation is the most frequent new-onset arrhythmia following TAVI. NOAF post-TAVI is associated with an increased risk of death and cerebrovascular events.(10) Colchicine has proven safe and effective in the prevention of atrial fibrillation after cardiac surgery. Randomized trials in patients after cardiac surgery found a relative risk reduction in the incidence of NOAF ranging between 20 and 50% if patients received perioperative treatment with colchicine as opposed to no treatment or placebo with notably higher effects in as treated analyses.(11)

The occurrence of atrioventricular conduction disturbances requiring the implantation of a permanent pacemaker is the most frequent complication after TAVI.(12) Injury to the AV node and left bundle branches due to a transient inflammation and tissue edema is an important mechanism involved in the development of conduction disturbances after TAVI.(13) The anti-inflammatory effects of colchicine(14) may mitigate the occurrence of atrioventricular conduction disturbances and thus the need for the implantation of a permanent pacemaker post TAVI.

The rationale of the present trial is to investigate the efficacy of colchicine for the prevention of NOAF and conduction disturbances requiring the implantation of a permanent pacemaker in patients undergoing TAVI.

Subclinical leaflet thrombosis of bioprosthetic aortic valves detected as hypo-attenuated leaflet thickening and reduced leaflet motion by means of four-dimensional volume-rendered computed tomography is frequent.(15) The clinical impact of subclinical leaflet thrombosis, in particular with respect to the risk of thrombo-embolic events and valve degeneration, is debated. Observational studies suggest that inflammatory processes may play a role in the development of HALT next to valve-specific, anti-thrombotic treatment and hemodynamics.(16) Hence, secondary exploratory analyses will evaluate whether the occurrence of subclinical leaflet thrombosis differs in patients treated with the anti-inflammatory agent Colchicin and those receiving placebo.

3.2 Investigational Product and Indication

Colchicine is an alkaloid interfering with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1β. Colchicine is indicated for the treatment of acute gout flares and familial Mediterranean fever. Colchicine is contraindicated in patients with hypersensitivity to the active substance or any of its excipients, with blood dyscrasias, or with renal or hepatic impairment and concomitant intake of Cyclosporine, Clarithromycin, Amiodaron, Omeprazol or other strong inhibitors of CYP3A4 or P-Glycoprotein. Adverse effects of colchicine include abdominal cramping, nausea, diarrhea, abdominal pain, vomiting, lactose intolerance, fatigue, headache, sensory motor neuropathy, alopecia, maculopapular rash, purpura, rash, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anaemia, elevated liver enzymes, myopathy, myotonia, muscle weakness, muscle pain, rhabdomyolysis, azoospermia, oligospermia. However, these adverse effects have been generally reversible upon temporarily interrupting treatment or lowering the dose of colchicine. Serious toxic manifestations associated with colchicine most often occur with excessive accumulation or overdosage.(17)

3.3 Preclinical Evidence

New onset atrial fibrillation (NOAF) in patients undergoing TAVI is multifactorial and probably involves systemic inflammation (18), atrial oxidative stress (19) and increased sympathetic tone (19, 20). Injury to the AV node and left bundle branches due to a transient inflammation and tissue edema is an important mechanism involved in the development of conduction disturbances requiring the implantation of a permanent pacemaker post TAVI.(13) Because colchicine possesses both anti-inflammatory and sympatholytic effects, it appears a logical candidate for the prevention of NOAF and conduction disturbances requiring the implantation of a permanent pacemaker.(14)

3.4 Clinical Evidence to Date

To date, there is no available evidence on the effect of colchicine intake on the incidence of NOAF or conduction disturbances requiring the implantation of a permanent pacemaker post TAVI. Evidence from the surgical literature indicates however a reduction of NOAF in patients treated with colchicine as compared with placebo, thus lending support to the hypothesis that reduction of post-procedural inflammation mitigates the occurrence of new onset rhythm disturbances.

Randomized trials in patients after cardiac surgery found a relative risk reduction in the incidence of NOAF ranging between 20 and 50% if patients received perioperative treatment with colchicine as opposed to no treatment or placebo with notably higher effects in as treated analyses.(11) According to a meta-analysis adverse drug-related effects, mainly gastrointestinal intolerance, were more frequently documented in patients treated with colchicine (21% vs. 8%). In contrast, there were no significant differences in the rates of major adverse events between the experimental and the control arm (3.2% in both groups).(11)

An observational study reported markedly lower rates of new pacemaker implantation in patients under anti-inflammatory therapy with steroids than patients without, a finding that supports the hypothesis that local inflammation may relevantly contribute to the occurrence of atrio-ventricular conductance disturbances and anti-inflammatory treatments may be able to reduce the need for new pacemaker implantation after TAVI.(21)

3.5 Dose Rationale: Rationale for the intended purpose in study (pre-market MD)

Colchicine will be administered in a loading dosage of 1mg single dose (=2x 0.5mg) per os the day before TAVI, followed by 1mg single dose (=2x 0.5mg) the day of the intervention. Thereafter, colchicine 0.5mg will be administered once daily per os continuously for 12 days post-TAVI. All RCTs comparing colchicine to placebo for the prevention of NOAF post cardiac surgery used 0.5mg or 0.6mg twice daily for the duration of one week to one month.(11) However, gastrointestinal problems were frequent (21%) and often severe enough to stop treatment. Moreover, our study population will be significantly older than patients undergoing cardiac surgery and mean peak plasma levels of colchicine were reported to be two times higher in elderly subjects compared to young healthy males. It is possible, that the higher exposure in the elderly subjects reflecting the greater frequency of decreased renal function, concomitant disease, or other drug therapy.(17) Approximately two-thirds of NOAF occurs during the first 48–96h post TAVI coinciding with the peak inflammatory response.(22) Although peak plasma concentrations occur 1 hour after administration, maximal anti-inflammatory effects develop over 24 to 48 hours, based on intra-leukocyte accumulation.(23) To ensure maximal anti-inflammatory effects at the time of the TAVI a loading dosage the day pre-TAVI will be administered as in several RCTs for the prevention of NOAF post cardiac surgery.(11)

3.6 Explanation for choice of comparator (or placebo)

As there is no established drug treatment for the prevention of NOAF and/or conduction disturbances requiring the implantation of a permanent pacemaker post TAVI a placebo will be used in the control group.

3.7 Risks / Benefits

Risk Analysis

- The most commonly reported adverse events of colchicine were gastrointestinal in nature (diarrhoea, nausea and vomiting). These side effects are mainly dose related and occurred at very low rate (not higher than placebo) when the drug was employed at the low regimen used in the current trial in the context of post-infarction patients.(24) Considering that patients with Inflammatory bowel disease or chronic diarrhea are excluded from participation, the risk of observing important and frequent side effects related to this drug taken for a maximum of 14 days is considered to be minimal.

- The study-specific CCTA performed 30 days after the procedure comprises exposure of patients to ionizing radiation and contrast agent. CCTA is the only available diagnostic test to capture subclinical leaflet thrombosis and leaflet-motion abnormalities of bioprosthetic aortic valves. With the most recent technology and new acquisition protocols, the radiation dose for the contrast-enhanced, cardiac CT scan with full cardiac-cycle coverage is 5 to 15mSv.(25) The scan will be performed according to the protocol used in clinical practice. Since patients with pre-existing kidney disease with a creatinine clearance ≤30 ml/min are excluded, additional contrast exposure is not expected to result in additional kidney injury in our patient

population.

3.7.1 Main Side Effects of Colchicin:

As with any subject undergoing medical therapy with colchicine, subjects in this study may experience adverse events and/or outcomes that may include, but are not necessarily limited to the following (26):

Frequently:

- Diarrhea
- Abdominal cramping
- Abdominal pain
- Vomiting
- Nausea
- Muscle weakness
- Fatigue
- Sensory motor neuropathy

Occasionally:

- Leukopenia
- Granulocytopenia
- Thrombocytopenia
- Aplastic anaemia
- Allergic reaction
- Alopecia
- Pruritus
- Purpura
- Onychodystrophia
- Kidney injury

Very rarely:

- Stevens-Johnson-Syndrom
- Elevated liver enzymes
- Myopathy
- Rhabdomyolysis

Patients will undergo thorough pre-procedural assessment prior to selection and inclusion into the study. Following randomization, patients will be closely monitored by their physicians. Careful medical follow-up is required for detection and adequate management of potential complications.

3.7.2 Benefits

Patients will have no known or guaranteed benefit from participating in the trial. Patients will be monitored more closely than in normal clinical routine which might bring a benefit for individual health.

The benefits to be evaluated within this study for the colchicine group fall into the following categories:

- Decreased risk for significant conduction disturbances post TAVI and therefore a decreased risk for the requirement of a permanent pacemaker.
- Decreased risk for NOAF post TAVI and therefore potentially a decreased risk of death and cerebrovascular events.(10)
- Close and precise follow-up of rhythm disturbances after hospital discharge through prolonged rhythm monitoring.

3.8 Justification of choice of study population

The study population consists of patients referred for treatment of symptomatic severe aortic stenosis and selected to undergo TAVI by the heart team. In this cohort, NOAF or atrioventricular conduction disturbances requiring the implantation of a permanent pacemaker is expected to occur in almost half of the patients.(10, 12)

4. STUDY OBJECTIVES

4.1 Overall Objective

The overall objective of the present study is to investigate the efficacy of peri-procedural administration of colchicine for the prevention of NOAF and conduction disturbances requiring the implantation of a permanent pacemaker in patients undergoing TAVI.

4.2 Primary Objective

The primary objective is to investigate whether colchicine reduces the composite of NOAF or the occurrence of conduction disturbances requiring the implantation of a permanent pacemaker in the first 30 days post TAVI.

4.3 Secondary Objectives

The secondary objectives are to investigate:

- The incidence of NOAF (at 30 days, 1 year).

- The incidence of conduction disturbances requiring the implantation of a permanent pacemaker (at 30 days, 1 year).

- The incidence and predictors of conductance disturbances: new or worsened first-degree atrioventricular (AV) block, second-degree AV block (Mobitz I or Mobitz II), high-grade atrioventricular block, third-degree AV block, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block, intraventricular conduction delay (at 30 days, 1 year).

- The incidence of new arrhythmias resulting in hemodynamic instability or requiring therapy (defined as electrical/medical cardioversion or initiation of a new medication e.g. oral anticoagulation, rhythm, or rate controlling therapy) (at 30 days, 1 year).

- The difference in inflammatory marker levels in patients treated with colchicine or placebo at day 1 post TAVI.

- The proportion of patients with at least one prosthetic leaflet with > 50% motion reduction or with at least one prosthetic leaflet with thickening (at 30 days).

- The proportion of prosthetic leaflets with > 50% motion reduction or leaflet thickening (at 30 days).

- The incidences of major clinical adverse events such as all-cause mortality, stroke, transient ischemic attack, bleeding event, kidney injury, systemic embolism, myocardial infarction, infections, clinical valve thrombosis at 30 days and 1 year post-TAVI in patients treated with colchicine or placebo.

4.4 Safety Objectives

The study aims to assess the tolerability of the applied colchicine dose in terms of incidence of gastrointestinal side effects and clinically severe side effects (see 5.3).

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome will be a composite of NOAF or the occurrence of conduction disturbances requiring the implantation of a permanent pacemaker in the first 30 days post TAVI in patients treated with colchicine or placebo.

5.2 Secondary Outcomes

The secondary outcomes will be:

- The incidence of NOAF (at 30 days, 1 year).

- The incidence of conduction disturbances requiring the implantation of a permanent pacemaker (at 30 days, 1 year).

- The incidence and predictors of conductance disturbances: new or worsened first-degree atrioventricular (AV) block, second-degree AV block (Mobitz I or Mobitz II), high-grade atrioventricular block, third-degree AV block, right bundle branch block, left bundle branch block, left anterior fascicular block, left posterior fascicular block, intraventricular conduction delay (at 30 days, 1 year).

- The incidence of new arrhythmias resulting in hemodynamic instability or requiring therapy (defined as electrical/medical cardioversion or initiation of a new medication e.g. oral anticoagulation, rhythm, or rate controlling therapy) (at 30 days, 1 year).

- The difference in inflammatory marker levels in patients treated with colchicine or placebo at day 1 post TAVI.

- The proportion of patients with at least one prosthetic leaflet with > 50% motion reduction or with at least one prosthetic leaflet with thickening (at 30 days).

- The proportion of prosthetic leaflets with > 50% motion reduction or leaflet thickening (at 30 days).

- The incidences of major clinical adverse events such as all-cause mortality, stroke, transient ischemic attack, bleeding event, kidney injury, systemic embolism, myocardial infarction, infections, clinical valve thrombosis at 30 days and 1 year post-TAVI in patients treated with colchicine or placebo.

5.3 Safety Outcomes

Incidence of gastrointestinal side effects and clinically severe side effects possibly related to study drug intake. (26)

Frequently:

- Sensory motor neuropathy

Occasionally:

- Leukopenia
- Granulocytopenia
- Thrombocytopenia
- Leukopenia
- Aplastic anaemia
- Allergic reaction
- Acute kidney injury

Very rarely:

- Stevens-Johnson-Syndrom
- Myopathy
- Rhabdomyolysis

6. STUDY DESIGN

6.1 General study design and justification of design

Co-STAR is an investigator-initiated, randomized, double-blind, placebo-controlled, clinical trial. A total of 200 patients referred for treatment of symptomatic severe aortic stenosis and selected to undergo transfemoral TAVI by a heart team decision will be randomized in a 1:1 ratio to the treatment with colchicine or placebo by a computer-based randomization process. Trial participants, care providers, outcome assessors, and data analysists will be blinded to the treatment allocation. Patients will be treated with colchicine in a loading dosage of 1mg single dose (=2x 0.5mg) or placebo the day before TAVI, 1mg single dose (=2x 0.5mg) colchicine or placebo the day of the procedure, and colchicine 0.5mg or placebo once daily thereafter up to post-procedural day 12. Inflammatory laboratory markers will be measured in blood drawn at post-procedural day 1. Blood will be drawn at the time of routine post-procedural blood withdrawal and results will be stored separately to avoid potential unblinding of study personnel. Patients will be continuously tele-monitored for rhythm disorders up to discharge. At discharge, a 7-day long-term rhythm monitoring will be conducted. A clinical follow-up will be performed at 30 days and will include clinical endpoint ascertainment, assessment of long-term rhythm monitoring, CCTA, ascertainment of current medical treatment, capture of potential drug-related adverse effects, 12-lead ECG and monitoring of the patient's blood count, hepatic and renal function,. Follow-up at 1 year will comprise clinical endpoint and current medical treatment ascertainment, a 12-lead ECG (performed on-site or by referring physician) and will be complemented by routine data collection either in connection with the Swiss TAVI-Registry (clinicaltrials.gov, NCT01368250) or study specifically, if patient is not participating in the Swiss TAVI Registry.

Subject participation is expected to be 1 year, total trial duration is estimated at 4.5 years.

6.2 Methods of minimising bias

6.2.1 Randomisation

Randomisation will be performed after heart team decision, all eligibility criteria have been checked, and written informed consent has been obtained. The allocation schedule is based on block randomization (block size of 8) and will be stratified on presence or absence of right bundle branch block to prevent unequally balanced groups with regard to the known risk factors for the development of conduction disturbances requiring the implantation of a permanent pacemaker. Each patient will be assigned a unique identification number, which will be linked to all recorded trial data providing encrypted data of the individual for data analysis.

6.2.2 Blinding procedures

Placebo tablets specifically prepared for this trial will be capsuled the same as the IMP and thus will be identical to the real drug in color, appearance, taste of capsule, as well as packaging and labelling. Trial participants, care providers, outcome assessors, and data analysists will be blinded to the assignment of treatment.

6.2.3 Other methods of minimising bias

The treatment allocation will be known only to the Bern University Hospital Pharmacy (ISPI), which prepares the study medication. Both colchicine and placebo encapsulated tablets will be provided in identical boxes with identical labels. The University Hospital Pharmacy (ISPI) will take care of the preparation and labelling of the study drug and placebo. Neither the statistician, nor the data manager, nor any other study personnel, nor physicians will have access to the list decoding treatment allocation.

Blood samples drawn on post-procedural day 1 for assessment of inflammatory markers will be analyzed immediately but the results will be stored separately in order to prevent potential earlier unblinding based on the laboratory results.

6.3 Unblinding Procedures (Code break)

For necessary unblinding sealed envelopes per randomization number / box number are kept in a separate folder with the Investigator Site File. An authorized investigator can thus unblinde at any time necessary. The key to the Patient ID and Randomisation Number are kept in the Investigator Site File (Master Subject List). Note: Although possible, we do not expect the need for emergency unblinding as there is no known specific antidote, and colchicine is not effectively removed by dialysis. The effect lasts irreversibly after intake until clearance by the body.

7. STUDY POPULATION

The trial will be conducted at a tertiary high-volume cardiology centre in Switzerland. 200 subjects will be recruited from patients presenting at or being referred to the corresponding institution due to symptomatic severe aortic stenosis requiring intervention, if they are regarded to be better candidates for TAVI than for SAVR by the Heart Team based on risk scores, comorbidities and frailty assessment. Patients fulfilling the clinical inclusion criteria, not meeting exclusion criteria and having provided written informed consent will be enrolled and constitute the study population.

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

1. Age ≥ 65 years
2. Symptomatic severe aortic stenosis defined by an aortic valve area (AVA) ≤1.0 cm^2 or an AVA indexed to body surface area <0.6cm^2/m^2
3. Selected to undergo transfemoral TAVI based on heart team decision

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

1. Life expectancy <1 year irrespective of valvular heart disease
2. Kidney disease with a creatinine clearance ≤30 ml/min
3. Known severe liver disease
4. Known neuromuscular disease
5. Clinically significant anaemia with haemoglobin <80g/L
6. Known inflammatory bowel disease or chronic diarrhea
7. Known ongoing bacterial infection
8. Known galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
9. Current treatment with colchicine, steroids or biologicals for any indication
10. Concomitant intake of Cyclosporine, Amiodaron, Clarithromycin, Erythromycin, Omeprazol, Verapamil or other strong inhibitors of CYP3A4 or P-Glycoprotein
11. Concomitant intake of Carbamazepin, Phenobarbital, Phenytoin, Rifampicin or other strong inductors of CYP3A4 and P-Glycoprotein
12. Permanent pacemaker or implantable cardioverter defibrillator
13. History of atrial fibrillation
14. Absence of sinus rhythm on hospital admission
15. Planned non-cardiac surgery within 30 days
16. Known intolerance to colchicine
17. Inability to provide informed consent
18. Known or suspected non-compliance, drug or alcohol abuse
19. Participation in another clinical trial with an active intervention
20. Any other planned cardiac intervention performed in the 7 days before TAVI, concomitantly with TAVI or in the 30 days after TAVI except for percutaneous coronary interventions.

7.2 Recruitment and screening

At the participating site, patients presenting with symptomatic severe aortic stenosis and agreed upon TAVI by transfemoral access being the recommended treatment modality by the Heart Team will be screened for inclusion and exclusion criteria based on the clinical presentation, findings of echocardiographic and electrocardiographic assessments. Eligible subjects will then be informed about the purpose and course of the study through the investigators or their designees and the patient information sheets will be handed out together with the informed consent form as described in section 2.6. If a patient is eligible, willing to participate and has signed the informed consent form, he/she can be enrolled in the trial.

7.3 Assignment to study groups

Eligible patients will be assigned to the treatment with colchicine or placebo at a 1:1 ratio. Block randomisation will be done by ISPI using a computer-based randomization process as described in section 6.2.1. The IMP box number indicated on the label is unique and will be allocated in numerical order according the stratification arm to a subject. Each patient will be assigned a unique identification number, which will be linked to all recorded trial data providing encrypted data of the individual for data analysis.

7.4 Criteria for withdrawal / discontinuation of participants

Patients will be encouraged to remain in the trial until completion of the 1-year follow-up.

Full withdrawal: Patients enrolled in the trial are allowed to withdraw from the study at any time. Patient will be encouraged to send back the remaining IMP/Placebo as well as to participate in the visits. A final telephone interview should be performed if possible to capture and document the reason for withdrawal whenever possible, although the patient can withdraw without providing a reason for this step. These patients will be recorded as withdrawal of informed consent and declared accordingly in the patient flow chart.

Partial withdrawal: If patient does not want to be contacted anymore, patient will be asked orally if data can be collected at the general practitioner at follow up windows or if full withdrawal is wished. If data can be collected at the general practitioner at follow up windows patient will be marked as “partial-withdrawal” and available data will be collected at local physician.

Further reasons for discontinuation of subjects after enrolment are loss to follow-up and death. A patient is not considered lost to follow up until one full year post-TAVI have elapsed and investigators will try to contact the patient at every planned follow-up. If a patient refuses further follow-up examinations or is lost-to follow-up, the patient will be censored at the time when the last follow-up interview or examination took place. In case of death, the cause should be determined by consulting corresponding medical records or contacting the physician, who issued the death certificate. All deaths are considered cardiovascular unless an unequivocal non-cardiovascular cause can be established.

Patient survival status will be collected over public sources.

Patient Data will be collected until the time point of withdrawal or as defined above and kept encrypted until final data analysis and publication is completed. Thereafter, the key will be destroyed.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products

8.1.1 Experimental Intervention (treatment)

Colchicine 0.5mg, a pill, which is taken per os.

8.1.2 Control Intervention (standard/routine/comparator treatment)

Placebo, a pill (same colour, same form as the investigational product), which is taken per os.

8.1.3 Packaging, Labelling and Supply

Both colchicine and placebo encapsulated tablets will be provided in identical boxes with identical labels; all study participants will receive the supply for the entire study duration of 12 days post-TAVI.

Import, Capsulation and labelling of IMP/Placebo are in the responsibility of the Institut für Spitalpharmazie, Inselspital Bern (full contact details see section 1.7).

8.1.4 Storage Conditions

Colchicine supplies is kept in a secure, limited access storage area under standard recommended storage conditions. Supply, storage, return or destruction are performed according to standard procedures.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

Colchicine will be administered in a loading dosage of 1mg single dose (=2x 0.5mg) per os the day pre-TAVI and 1mg single dose (=2x 0.5mg) at the day of procedure. Afterwards, colchicine 0.5mg will be administered once daily per os continuously up to post-procedural day 12..

First IMP administration should whenever possible take place 20-28 hours before TAVI but not less than 12 hours before second IMP administration and following TAVI.

In case of severe adverse side effects of the study drug or placebo, participant request, toxic symptoms such as nausea, vomiting, abdominal pain or diarrhea as well as signs or symptoms that could indicate a blood cell dyscrasia, such as fever, stomatitis, sore throat, or prolonged bleeding the study drug will immediately be discontinued.

8.2.2 Control Intervention

Placebo will be given once daily per os the day pre-TAVI and once daily per os continuously up to post-procedural day 12.

8.3 Compliance with study intervention

Patients will be asked to return unused medication for pill count. Patients are provided with a diary to document IMP/Placebo intake. In case necessary study nurse might call patient to remind the patient about IMP/Placebo intake.

8.4 Data Collection and Follow-up for withdrawn participants

All data of withdrawn participants will be collected and used for analysis up to the point in time of withdrawal.

Ongoing SAE, or any ongoing AEs of laboratory values or of vital signs being beyond the alert will be followed-up within the study until the adverse event resolves or until a stable clinical endpoint is reached. For this purpose, general practitioner might be involved in case the patient refuses to be contacted by study personnel. This data will also be collected and evaluated within the study.

Patient data will be kept encrypted after withdrawal until study completion. Data will be anonymized by destruction of the key before archiving.

Trial specific preventive measures

Concomitant treatment with Cyclosporine, Clarithromycin, Amiodaron, Omeprazol or other strong inhibitors of CYP3A4 or P-Glycoprotein are not permitted during the first 14 days of the study and intake of grapefruit should be avoided. We expect no impact on the primary objective of our study from this measure.

8.5 Concomitant Interventions (treatments)

Percutaneous coronary interventions are permitted before, concomitantly, or after TAVI. No other planned cardiac interventions are permitted concomitantly or in the 30 days after TAVI.

8.6 Study Drug Accountability

The University Hospital Pharmacy (ISPI) takes care of the labelling of the study drug and placebo.

Drug Accountability will be in detail documented on corresponding drug accountability log(s), patient diary and pill count upon return of IMP/Placebo at study visits.

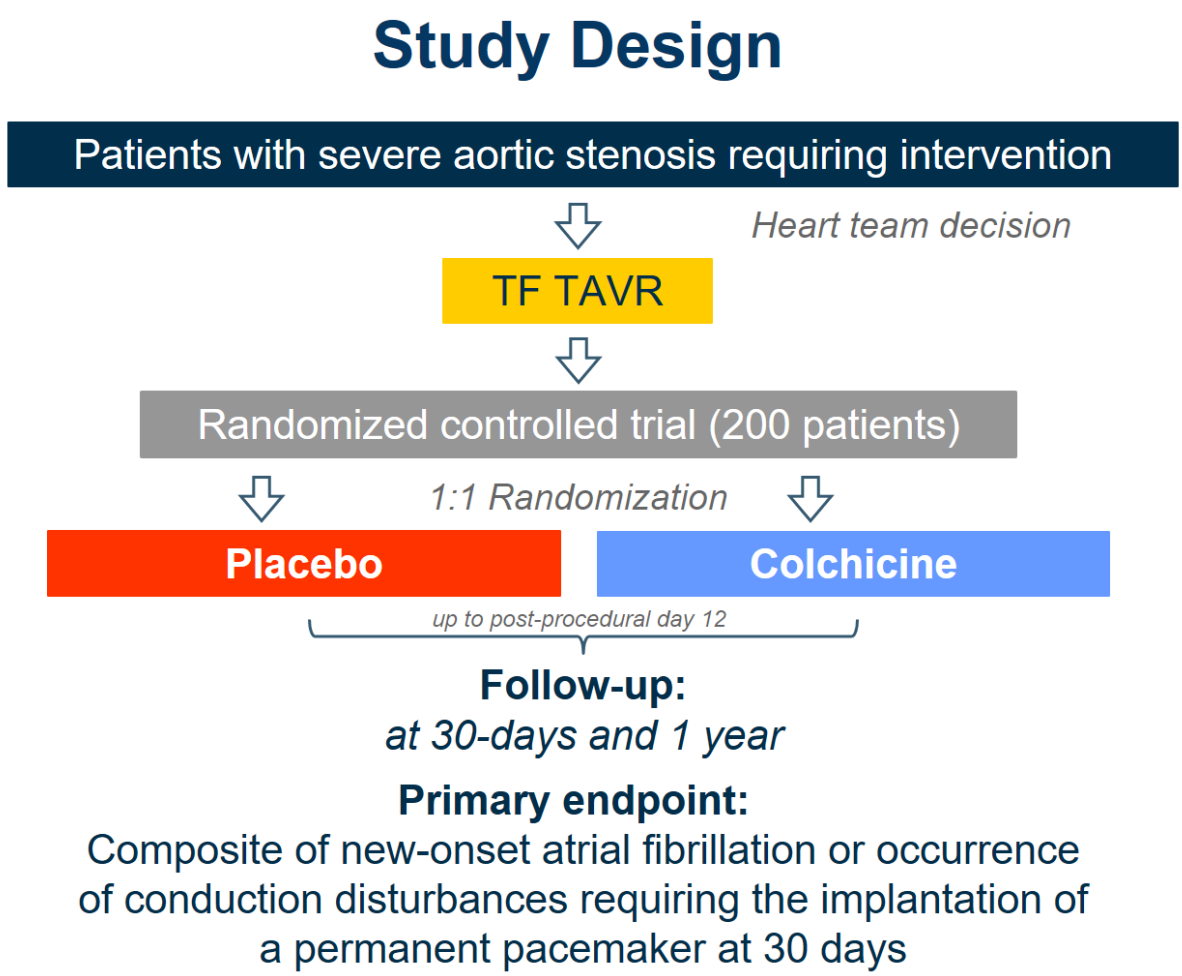
8.7 Return or Destruction of Study Drug

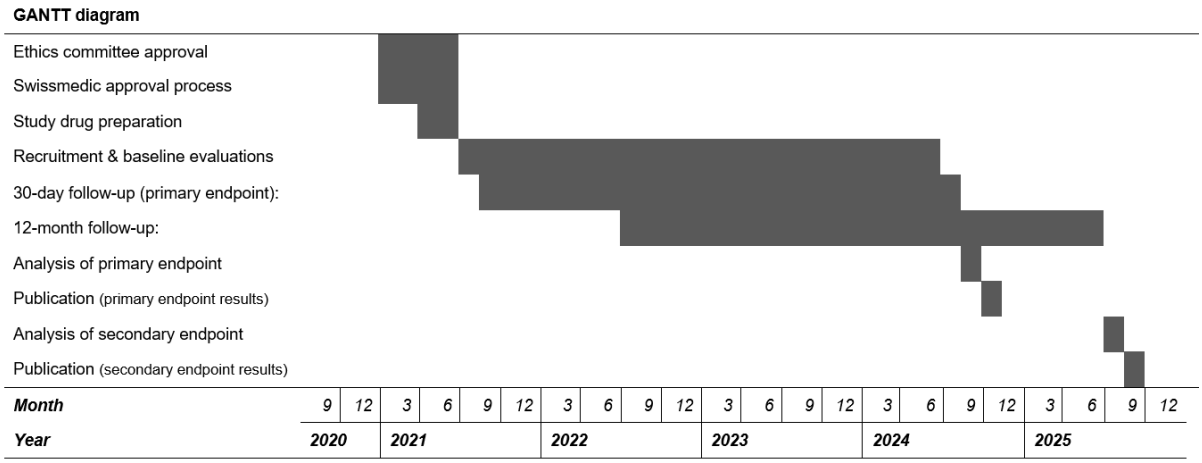
IMP/Placebo will be destroyed according standard procedure by Institut für Spitalpharmazie, Inselspital Bern.

9. STUDY ASSESSMENTS

Follow-up evaluations will take place at 30 days and 1 year. All periods are defined in reference to the day of the TAVI. Upon completion of the final protocol assessment or in case of withdrawal of a patient, subject participation will be considered complete and the patient should then be followed per the local standard of care for their condition.

9.1 Study flow chart(s) / table of study procedures and assessments





See also “STUDY SCHEDULE” (Page 15).

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

The incidence of new-onset atrial fibrillation (NOAF) will be assessed based on extended rhythm monitoring performed until 7 days post-discharge as well as clinically or incidentally captured episodes of NOAF captured during routine care thereafter. NOAF is defined as at least one episode of atrial fibrillation with a duration >30s.

The incidence of conduction disturbances requiring the implantation of a permanent pacemaker will be assessed at 30 days. Conduction disturbances requiring the implantation of a permanent pacemaker include second-degree AV block type 2 (Mobitz II), second-degree AV block type 1 (Mobitz I) which causes symptoms, 2:1 AV block in the presence of a QRS ≥120ms, ≥2 consecutive P waves at a constant physiologic rate that do not conduct to the ventricles, third-degree AV block, alternating bundle branch block and in the setting of AF, a prolonged pause (>3 s) or a fixed slow (<50 beats/min) ventricular response rate.(27, 28).

9.2.2 Assessment of secondary outcomes

The incidence of new-onset atrial fibrillation (NOAF) will be assessed based on extended rhythm monitoring performed until 7 days post-discharge as well as clinically or incidentally captured episodes of NOAF captured during routine care thereafter.

The inflammatory marker levels will be measured in blood drawn on day 1 post-TAVI.

The incidences of conduction disturbances requiring the implantation of a permanent pacemaker, major clinical adverse events (such as all-cause mortality, stroke, transient ischemic attack, bleeding event, kidney injury, systemic embolism, myocardial infarction, infections, clinical valve thrombosis), other conductance disturbances and new arrhythmia resulting in hemodynamic instability or requiring therapy will be assessed at 30 days as part of the clinical follow up visit and at 1 year by routine data collection in connection with the Swiss TAVI-Registry (clinicaltrials.gov, NCT01368250) or study specifically, if patient is not participating in the Swiss TAVI Registry.

The hypo-attenuated leaflet thickening and leaflet-motion abnormalities of the bioprosthetic aortic valves will be based on a study-specific CCTA (performed according to protocol used in clinical practice) at 30 days and assessed by radiologists blinded to treatment allocation.

9.2.3 - Assessment of other outcomes of interest

At 30 days a clinical follow up will take place, which will further include: ascertainment of current medical treatment, ascertainment of clinical status, ascertainment of adherence to the IMP, 12-lead electrocardiogram,transthoracic echocardiography and monitoring of blood count, hepatic and renal function.

Ascertainment of current medical treatment, ascertainment of clinical status, 12-lead electrocardiogram and transthoracic echocardiography will be assessed at 1 year by routine data collection in connection with the Swiss TAVI-Registry (clinicaltrials.gov, NCT01368250) or study specifically, if patient is not participating in the Swiss TAVI Registry.

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events

The following event information will be collected for any adverse event occurring up to post-procedural day 12 and any adverse event listed under 5.3 as well as any SAE occurring up to one year after TAVI: time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with study treatment; definition of AE and procedures are outlined in Section 10. We will inquire for the occurrence of adverse events during each follow-up visit using structured interviews. Spontaneous reports will be collected from primary care physicians and referring hospitals.

9.2.4.2 Laboratory parameters

Laboratory parameters will be collected according to clinical routine as clinically indicated with the exception of predefined analyses on day 1 after TAVI. In addition, we will regularly monitor the patient's blood count, hepatic and renal function every day until hospital discharge (mean duration of hospitalization according to Swiss TAVI registry 9.3 ± 5.8 days) as well as part of the clinical follow up

at 30 days. Abnormal laboratory parameters potentially related to the IMP/Placebo intake will be recorded as adverse events.

9.2.4.3 Vital signs and ECGs

Heart rate, blood pressure and ECG will be collected according to clinical routine at the 30 days follow-up.

9.2.5 Assessments in participants who prematurely stop the study

Participants who prematurely stop the IMP intake will be asked to participate in the regular follow-ups including all planned clinical and procedural steps.

9.3 Procedures at each visit

9.3.1 Screening visit, Day -30 to -1.

- Patient Information and Informed Consent*
- Demographics
- Medical History
- In-/Exclusion Criteria*
- Physical Examination
- Vital Signs
- Laboratory Tests
- Randomisation*
- ECG
- TTE
- Collection of Routine data

9.3.2 Visit 1 (during in-hospital stay), Day -1

- Medical History
- Physical Examination
- Vital Signs
- Laboratory Tests
- ECG
- Administer Study Medication*
- Collection of Routine data
- Monitoring of adverse and serious adverse events

9.3.3 Visit 2 (during in-hospital stay), Day 1 until discharge

- Medical History
- Vital Signs
- ECG
- TTE
- Laboratory Tests*
- Adverse Events*
- Continued rhythm monitoring*
- Continued Study Medication intake*
- Scheduling next follow-up*
- Collection of Routine data
- Monitoring of adverse and serious adverse events*

9.3.4 After discharge until day 30

- Continued rhythm monitoring for first 7 days after discharge*
- Continued study medication intake until post-TAVI day 12*
- Monitoring of adverse and serious adverse events*

9.3.5 Visit 3, Day 30-37

- Vital Signs
- Medical History
- ECG
- TTE
- CCTA*
- Monitoring of adverse and serious adverse events*

- Laboratory Tests*
- Primary and secondary outcome assessment*
- Collection of Routine data

9.3.6 Visit 4, 1 year (+ 21 days)

- Standardized telephone interview for clinical endpoint ascertainment (secondary outcomes)*
- Medical History
- 12-lead ECG
- Monitoring of adverse and serious adverse events*
- Collection of Routine data
- Available routine data will be collected (e.g. TTE) as per Swiss TAVI registry, and FUP, if possibly, will be combined with the FUP for the Swiss TAVI registry, if patient is participating in the Swiss TAVI registry.

* Study specific procedure

10. SAFETY

10.1 Drug studies

According the study schedule (page 15), specified adverse events that might be drug related (see listing 5.3) and all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship

	Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (Product Information for approved drugs, respectively).

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is probably or possibly related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

Reporting of SAEs to Sponsor: The local Investigator will report all Serious Adverse Events (SAEs) regardless of the relationship to the investigated medicinal product to the Sponsor within 24 hours of becoming aware of the event. Events will be reported by entering the event into the eCRF. If eCRF is not available events can be provided to Sponsor by email and entered in the eCRF as soon as possible for independent assessment.

Please note: If not all information regarding the event is known within the first 24h or if final assessment by local investigator is not available within 24h the SAE will be reported anyways and missing information will be provided as soon as possible.

Reporting to CEC/CA SAE/SUSAR as defined per section 2.3.

Reporting and Handling of Pregnancies

Participant’s age ≥ 65 years is an inclusion criteria and pregnancies are thus excluded.

10.1.3 Follow up of (Serious) Adverse Events

The follow-up of participants terminating the study (either regularly or prematurely) with reported ongoing SAE, or any ongoing AEs of laboratory values or of vital signs being beyond the alert will be followed-up until the adverse event resolves or until a stable clinical endpoint is reached.

11. STATISTICAL METHODS

11.1 Hypothesis

The hypothesis with regard to the primary clinical endpoint is formulated as follows:

H0: P1 – P2 = 0

H1: P1 – P2 ≠ 0

P1 stands for the proportion of patients experiencing a primary outcome event among the subjects treated with colchicine and P2 the proportion experiencing an event among those treated with placebo.

The alternative and study hypothesis is that treatment with colchicine will be superior to treatment with placebo in reducing the composite cumulative incidence of new onset atrial fibrillation and the occurrence of conduction disturbances requiring the implantation of a permanent pacemaker at 30 days in patients undergoing TAVI (H1). H0 represents the null hypothesis stating that 30 days after transcatheter aortic valve implantation there is no difference in the cumulative incidence of the primary composite endpoint between the colchicine and placebo group.

11.2 Determination of Sample Size

According to preliminary results of a prospective study (ClinicalTrials.gov Identifier: NCT02559011), which included 150 patients who underwent TAVI and received an implanted loop recorder, the cumulative incidence of new onset atrial fibrillation after TAVI amounts to 25% at 30 days (unpublished data). The incidence of conductance disturbances requiring a permanent pacemaker implantation after TAVI amounts to 22 to 23% with devices of the self-expanding Evolut R Series and 10% with balloon-expandable devices. (30, 31)

Randomized trials in patients after cardiac surgery found a relative risk reduction in the incidence of NOAF ranging between 20 and 50% if patients received perioperative treatment with colchicine as opposed to no treatment or placebo with notably higher effects in as treated analyses.(11, 32)

Up to 59% of high degree atrio-ventricular blocks are reversible after TAVI,(33) transient inflammation and tissue edema is an important mechanism involved in the development of conduction disturbances after TAVI,(13) and an observational study reported markedly lower rates of new pacemaker implantation in patients under anti-inflammatory therapy with steroids than patients without.(21)

Based on a cohort predominantly treated with self-expanding transcatheter heart valves, we estimate the incidence proportion for the primary composite endpoint at 30 days at 42% in the control arm. Assuming a 45% relative risk reduction in the colchicine arm, the cumulative incidence is estimated at 23.1%. Based on these assumptions, 96 patients are required per study group to show superiority of the intervention with a power of 80% at two-tailed significance level of $\alpha = 0.05$. Accounting for a low attrition rate, 100 patients will be required per study group.

11.3 Statistical criteria of termination of trial

Asymmetric stopping boundaries will be used as stopping rules in the interim analysis performed after enrolment of 120 patients.

Pocock-type boundaries will be applied when monitoring for harm. If the interim-analysis shows harm for the colchicine group with a Type I error rate of 0.029 or smaller with respect to any of the following endpoints, the trial will be stopped:

- the primary composite endpoint
- all-cause mortality
- any stroke
- infections requiring prolonged index hospitalization or re-hospitalization

Stopping rules for the trial due to benefit of the colchicine administration will adhere to the Peto boundaries with a required p-value of 0.001 or smaller for the difference in the primary endpoint rate at 30 days in the interims-analysis.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

Primary analyses will be conducted according to the intention-to-treat (ITT) principle meaning that patients will be analyzed based on the treatment arm to which they were originally allocated to, irrespective of any crossing-over or treatment protocol violations.

Sensitivity analyses regarding the primary endpoint will be performed in the as-treated population, whereby patients will be analysed according to whether they have been taking the study medication for the first 7 days after initiation or not.

11.4.2 Primary Analysis

Primary analyses will take place after all patients will have completed 30-day follow-up and will be performed according to the intention-to-treat principle. The superiority assumption with regard to the primary endpoint will be tested by means of the risk difference between the colchicine and the placebo group at a two-sided significance level with a type I error rate of $\alpha = 0.05$.

11.4.3 Secondary Analyses

Further comparisons between the two treatment groups will be performed on demographical, clinical, electrocardiographically, imaging (echocardiography and computed tomography) as well as procedural characteristics. Continuous variables will be presented as mean ± standard deviation or median and interquartile range depending on their distribution. Categorical variables will be stated as number and proportion. Characteristics will be compared between the two treatment groups by means of unpaired t-tests for continuous variables and chi-square tests or Fisher's exact tests for categorical variables. Reported p-values will be two-sided. If a normal distribution cannot be assumed nonparametric tests will be considered to compare patient characteristics.

A sensitivity analyses with regard to the primary endpoint will be conducted in the as-treated population. Further secondary analyses will be performed in the intention-to-treat and as-treated populations with regard to secondary clinical and electrocardiographic endpoints at 30 days and 1 year. Pre-specified subgroup analyses with appropriate interaction tests will evaluate the effect of colchicine on the primary composite endpoint stratified by sex, valve-type, device-landing zone calcification, pre- and postdilatation, and presence or absence of right-bundle branch block at baseline.

11.4.4 Interim analyses

An interim analysis will be performed after 120 patients will have been randomized and completed 30-day follow-up. Statistical criteria of termination of the trial are defined in section 11.3. The analysis will be conducted by an independent statistician not involved in the trial analysis. The results of the interim analysis will be unblinded only after completing the predefined analyses. In case stopping criteria are reached, the Sponsor Investigator will be informed, otherwise interim-analyses will be made available only to the data and safety monitoring board.

11.4.5 Safety analysis

Analysis of the incidence of safety outcomes as listed in section 5.3 will be performed by DSMB (see section above). Analyses will be performed by an independent statistician and results made available for evaluation to the data and safety monitoring board in unblinded fashion.

11.4.6 Deviation(s) from the original statistical plan

Should statistical analyses deviate from the original statistical plan, this will be thoroughly described and justified in a protocol amendment, the publication of results and the final report.

11.5 Handling of missing data and drop-outs

If a patient withdraws from the study or is lost to follow-up, the subject will be censored at the time when the last follow-up examination took place. Analyses will be performed according to the complete case principle assuming that data from patients, who do not undergo the follow-up examination, will be missing completely at random.

12. QUALITY ASSURANCE AND CONTROL

The Sponsor/ Steering Committee will implement a system to manage quality throughout all stages of the trial process.

12.1 Data handling and record keeping / archiving

12.1.1 Case Report Forms

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system (eCRF/ REDCAP). After being trained on correct completion of the eCRF, investigators, their designees and assigned personnel will be authorized to enter data into the eCRF using a personal account. Data entry should be performed in a timely manner.

Subjects will be identified only by their assigned study number and year of birth on all eCRFs.

- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number) on each subject. The Patient Identification List always remains on site under restricted access under the responsibility of the local PI.
- The trial team will maintain all source documents in strict confidence.
- CRF entries will be performed by authorized persons and it will be assured that any authorized person can be identified.
- Responsibility for hosting the EDC system and the database lies with the Sponsor.

12.1.2 Specification of source documents

Source data must be available at the site to document the existence of the study participants and for purposes of data verification by sponsor-representatives, monitors, auditors, inspectors or representatives of local ethics committee. For each enrolled subject original or certified copies of all documents relating to the study as well as the medical treatment and medical history will be recorded and maintained in a medical file. These medical records constitute the source data and contain but are not limited to the following information:

- Original signed patient informed consent form of all enrolled patients
- Date of enrollment/ randomization
- Medical history/physical condition of the study patient before involvement in the study sufficient to verify investigational plan in- and exclusion criteria
- Medical records
- Assigned patient number (Subject Identification List)
- AE/SAE reported and their resolution, including supporting documents such as discharge summaries, investigation reports, lab results.
- Study patient’s condition upon completion of or withdrawal from the study.

A Source Data Location List (SDLL) must be maintained by the study site to facilitate source data verification and GCP compliance.

12.1.3 Record keeping / archiving

All trial records must be archived at the investigation centers for a minimum of 10 years after study end or premature termination of the clinical trial. Trial Master File will be archived for 10 years at Sponsor Site.

12.2 Data management

12.2.1 Data Management System

An electronic Clinical Data Management System (CDMS) will be applied (REDCAP). The eCRF will constitute the backbone of trial data; in addition de-identified source documents, electrocardiographies angiograms, computed topographies and echocardiographies may be uploaded. Upon completion of the eCRFs with regard to each stage of analysis (interim-analysis, safety analysis, primary and secondary analyses), the trial data will be forwarded to the statistician for analysis.

12.2.2 Data security, access and back-up

Subjects data will be linked to the patient only via a unique identification number and initials and year of birth when entered into the CDMS. The information, which decodes the patients' identity will not be stored online and will be kept in a safe, locked room with access restricted to study personnel. Data in the CDMS will be appropriately protected from malicious attacks by viruses and hackers to prevent that sensitive information is exposed to unauthorized persons and the IT security systems will be regularly reviewed. Furthermore regular backups will be conducted to avoid loss of data in case of malfunction of the server.

12.2.3 Archiving

Data will be extracted and stored on a hard-drive or DVD with the Trial Master File for 10 years after study completion. TMF and CRF data will be stored at Insel Gruppe AG, Inselspital Bern, Universitätsklinik für Kardiologie, Archiv Güterstrasse (location might change during the course of trial and archiving.)

12.2.4 Electronic and central data validation

During on-site monitoring-visits source data will be verified and data captured in the database validated against source data.

12.3 Monitoring

Monitoring will be defined by Insel Gruppe AG, Universitätsklinik für Kardiologie, Inselspital Bern. Independent on-site Monitoring will be performed by Clinical Trial Unit Bern.

Monitoring activities are in detailed defined per Monitoring Plan.

Monitors will periodically verify the conduct of the study and data collection to ensure that all activities are carried out according to the Clinical Trial Protocol, ICH-GCP E6(R2) and that source data quality and documentation as well data in the eCRF is accurate and complete (ALCOAC). For on-site visits the monitor will have access to subject records to perform verification of the source data and validate reports against source data. Investigators should be available to provide additional information on the study processes applied at the site. All involved parties must treat the participant data strictly confidential.

12.4 Audits and Inspections

Centre may be audited or inspected by the Ethics Committee or other applicable regulatory authorities during the course of the trial. Like the study monitors, the auditor or inspectors will be provided access to source data and eCRFs and the investigator will be available to answer questions. Again, all involved parties must treat the participant data strictly confidential and the Steering Committee should be notified of non-compliance of investigators with the study requirements to enable the introduction of appropriate actions.

12.5 Confidentiality, Data Protection

All data and information collected during this study related to the participating subject will comply with the standards for protection of privacy based on applicable local/ national requirements for subject's confidentiality. All data used in the analysis and summary of this study will be coded (without specific study subjects' names, address, date of birth, etc). Access to study subject files will be limited to authorised personnel of the Sponsor, the investigator, and research staff. Access to source documents and eCRFs will be permitted to regulatory authorities, the study monitor or sponsor representatives for purposes of monitoring, audits and inspections.

13. PUBLICATION AND DISSEMINATION POLICY

Principal authorship of primary publications will be held by the Steering Committee Members. Co-authorships will be ordered according to the level of contribution. Exceptions require the prior approval of the Steering Committee. Manuscripts from secondary analyses are anticipated with principal authorship held by study investigators in order of their contribution.

Reporting of results will follow guidelines according to the CONSORT 2010 statement.(34)

14. FUNDING AND SUPPORT

14.1 Funding

- Trial is funded by Universitätsklinik für Kardiologie, Inselspital Bern. Research grant for further studies might be applied for during the course of the study (SNF or other).
- The study is supported by: Bangerter-Rhyner-Stiftung and SwissLife

15. INSURANCE

Insurance will be provided by Insel Gruppe AG by Zurich Versicherung.

16. REFERENCES

Provide a list of the references cited in the protocol.

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17. APPENDICES

17.1 CCTA Protocol

Multislice cardiac CT angiography (CCTA) will be performed as previously published (Okuno T et al. Eur Heart J Cardiovasc Imaging. 2020;21(5):522-32.). In detail, after a routinely native CT scan of the heart for planning purpose, a standardized ECG gated CCTA covering the entire heart including the aortic valve, using spiral acquisition within 0-100% of RR on a Siemens Somatom Definition Flash Dual-Source scanner with a slice collimation of 128 × 0.6 mm, tube voltage of 100 or 120 kV, and tube current according to patient size (Siemens Medical Solutions, Inc., Forchheim, Germany) will be performed. Each patient receives an intravenous injection of 90 mL of contrast medium at a flow rate of 4 mL/s and image acquisition will be performed during an inspiratory breath-hold in a cranio-caudal direction. The standard scan will be performed using a bolus tracking technique for optimal scan acquisition time. Automatic current modulation (CareDose4D) will be used for raw data acquisition.