Protocol

Title: An Investigator-Initiated Prospective Randomized Open-Label Blinded-Endpoint Crossover Trial Comparing the Effect and Safety of **Flec**ainide and Metoprolol versus Metoprolol Alone to Suppress Ventricular Arrhythmias in **A**rrhythmic Mitral Valve **Pro**lapse (FLECAPRO).

EU CT No: 2022-500814-24-00

Sponsor: Oslo University Hospital, Oslo, Norway

Department of Cardiology

Chief of Department: Dr. Lars Aaberge

Principal Investigator: Dr Eivind Westrum Aabel

Oslo University Hospital

Contents

List of abbreviations

AE	adverse events
AESI	adverse event of special interest
BID	“bis in die”, two times a day
eCRF	electronic case report form
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ILR	implantable loop recorder
MDD	medical device deficiency
MVP	mitral valve prolapse
NSVT	non-sustained ventricular tachycardia
NYHA	New York Heart Association
PVC	premature ventricular complex
QD	“quaque die”, once a day
SAE	serious adverse events
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
WOCBP	women of childbearing potential

1.0 Protocol Summary

1.1 Protocol Synopsis

Protocol Title:	An Investigator-Initiated Prospective Randomized Open-Label Blinded-Endpoint Crossover Trial Comparing the Effect and Safety of Flecainide and Metoprolol versus Metoprolol Alone to Suppress Ventricular Arrhythmias in Arrhythmic Mitral Valve Prolapse.
Brief title:	Effect and safety of flecainide and metoprolol versus metoprolol alone to suppress ventricular arrhythmias in arrhythmic mitral valve prolapse
Sponsor:	Oslo University Hospital
Phase and study type:	Phase III, Prospective randomized open-label blinded-endpoint (PROBE) crossover trial
Investigational Compound:	Flecainide and metoprolol antiarrhythmic therapy versus the standard metoprolol antiarrhythmic therapy
Centers:	Oslo University Hospital, Rikshospitalet, Oslo, Norway
Study period:	Study start January 4th, 2023 Anticipated recruitment duration 3 years until January 31st, 2026 Last subject last visit (end-of-study): March 31st, 2028
Treatment duration:	13 months (metoprolol alone) and 13 months (flecainide + metoprolol)
Rationale:	Patients with arrhythmic mitral valve prolapse are at risk of life-threatening ventricular arrhythmias. To date, no medical therapy has shown to be effective in these patients. In general, beta blockers are considered first-line therapy, but treatment is often unsuccessful. Flecainide is an antiarrhythmic drug that is used to suppress ventricular arrhythmias in patients with structurally normal hearts, but is not studied in patients with arrhythmic mitral valve prolapse.
Objectives:	The main goal of this study is to evaluate the effect and safety of adding flecainide to standard beta blocker therapy to reduce burden

of ventricular arrhythmias in patients with arrhythmic mitral valve prolapse.

Primary Endpoint:

Number of ventricular tachyarrhythmias, composite of:

- Ventricular tachycardia
- Ventricular fibrillation

Secondary Endpoints:

Key secondary endpoints:

- Burden of premature ventricular complexes (by Holter monitoring)
- Health-related quality of life (number of patients with ≥5 points increase in SF-36 overall summary score)
- Number of severe ventricular tachycardias, composite of
    - Non-sustained ventricular tachycardia with syncope
    - Sustained ventricular tachycardia
    - Ventricular fibrillation

Secondary safety endpoints:

- Safety composite, composite of:
    - The number of adverse events
        - The number of adverse reactions
    - The number of serious adverse events
        - The number of serious adverse reactions
    - Higher degree AV-block (Mobitz type 2 or 3rd degree AV-block)

Exploratory secondary endpoints:

- Components of primary composite endpoint
    - Ventricular tachycardia
    - Ventricular fibrillation
- Components of key secondary endpoints
    - Burden of premature ventricular complexes

  - Health-related quality of life
  - Number of severe ventricular arrhythmias, composite of:
    - Non-sustained ventricular tachycardia with syncope
    - Sustained ventricular tachycardia
    - Ventricular fibrillation
- Left ventricular ejection fraction (change)
- Mitral regurgitation (change)
- N-terminal pro-B-type natriuretic peptide (change)
- NYHA class (change)
- Health-related quality of life as assess by the HADS questionnaire
- Per-protocol primary endpoint sensitivity analysis
- Intention-to-treat secondary safety endpoint sensitivity analysis

Study design: Active, single center, prospective, randomized open-label, blinded-endpoint (PROBE) crossover trial

Main inclusion criteria: Symptomatic arrhythmic mitral valve prolapse in patients 18 years of age or older at time of inclusion and clinical indication for antiarrhythmic therapy, with one of the following:

- PVC burden ≥3% per 24-hours.
- PVC burden ≥1% per 24-hours if occurring in bi-/trigemini and/or couplets, or if multifocal.
- Sustained or non-sustained ventricular tachycardia
- Aborted cardiac arrest

Main exclusion criteria: Strict contraindication for flecainide or metoprolol

Prior flecainide therapy

Concomitant use of inducers or inhibitors of CYP2D6, MAO inhibitors, or class I, III or IV antiarrhythmic drugs (other than flecainide)

Failure to obtain written informed consent

Sample size: 50 patients

Efficacy assessment: Implantable loop recorder, Holter monitoring, questionnaire

Safety assessment: Implantable loop recorder, Holter monitoring, ECG and physical visits

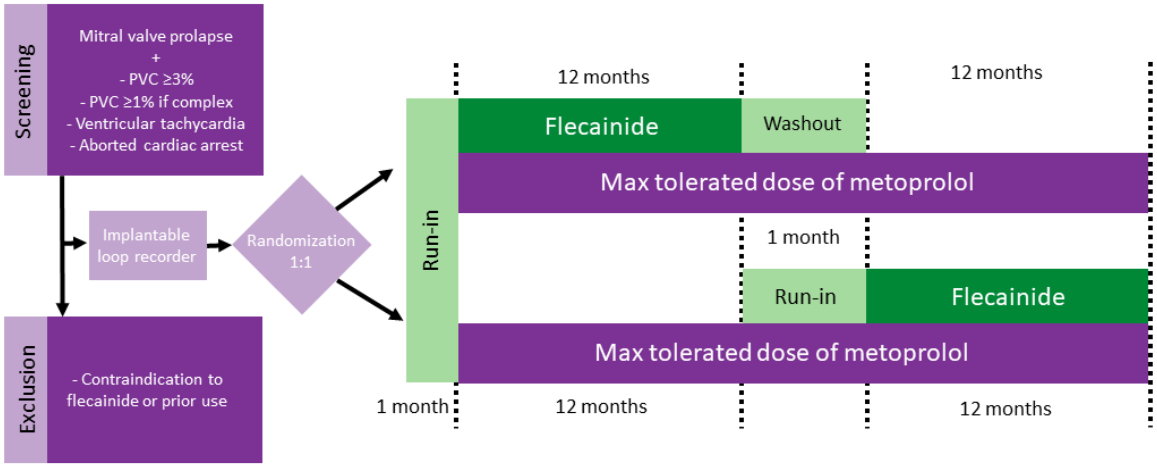

Figure 1. FLECAPRO study design

1.2 Schedule of Activities

Procedure	Screening (up to 6 weeks before 0)	1st treatment period (months)					2nd treatment period (months)				Discontinuation	Notes
		Washout and Run-in (1 month)		Treatment phase (12 months)			Washout and Run-in (1 month)	Treatment phase (12 months)			Early termination visit	
		0	0-1*	1	7	13 End of treatment visit	13-14*	14	20	26 End of treatment visit		Visits in the treatment phase are allowed to vary ±2 weeks. *Allowed to vary ±3 days.
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Physical Examination	X											
Medical History	X											
HRQoL questionnaire	X					X				X	X	SF-36 and HADS.
Concomitant Medication	X			X	X	X		X	X	X	X	
Laboratory Analysis	X			X	X	X		X	X	X	X	Hb, white blood cell count, platelet count, K, Na, glucose, HbA1c, creatinine, eGFR, ALT, AST, bilirubin, albumin, INR, NT-proBNP and troponin T.
Biobank		X				X				X		Extra blood will be appropriately labelled and stored in a biobank.
Flecainide serum concentration			X	X	X	X	X	X	X	X	X	Therapeutic range 200-1000 ng/ml (0.4-2.0 µmol/L).
Pregnancy Test		X					X			X		Only in WOBCP. Urinary pregnancy tests will be provided free-of-charge throughout the whole study.
Holter Monitoring	X			X	X	X		X	X	X	X	
Vital Signs	X			X	X	X		X	X	X	X	

12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	
Echocardiography	X					X				X	X	
Exercise ECG	X			X		X		X		X	X	
Cardiac magnetic resonance		X		X*						X**		If not contraindicated or performed within the last 24 months. *10 patients without prior ICD will perform CMR shortly after ILR implantation. **Last CMR will be done in participants randomized to flecainide in the second treatment period.
ILR Implantation		X										
Coronary Angiography	X											If not performed within the last 24 months prior to screening, we will perform a CT or invasive coronary angiography in patients with possible coronary artery disease according to guidelines in force.
Randomization		X										
Study drug distribution		X				X						
Collection of study intervention						X				X	X	Collection of metoprolol only after the last visit.
Evaluation of dose escalation			X				X					
Study Intervention		←	—	—	—	→	←	—	—	→		
Mandatory contraceptive use		←	—	—	—	—	—	—	—	→		Only in WOCBP. Until 3 days after discontinuation of study medication
Carelink™ Continuous Heart Rhythm Monitoring		←	—	—	—	—	—	—	—	→		
AE Review		←	—	—	—	—	—	—	—	→	X	
SAE Review		←	—	—	—	—	—	—	—	→	X	
Device Deficiency		←	—	—	—	—	—	—	—	→	X	

ECG = electrocardiogram, CMR = cardiac magnetic resonance, HRQoL = health-related quality of life, ILR = implantable loop recorder, AE = adverse event, SAE= serious adverse event.

2.0 Introduction

2.1 Study Rationale

Patients with arrhythmic mitral valve prolapse have frequent ventricular arrhythmias that are potentially life threatening[1-9], and there is no established medical treatment[8,9]. Flecainide, a drug primarily used to suppress atrial tachyarrhythmias[10], has shown to suppress ventricular arrhythmias in other cardiomyopathies[11-13], but its effect in patients with arrhythmic mitral valve prolapse has not been studied.

2.2 Background

Mitral valve prolapse (MVP) is a common condition[14,15] characterized by the bulging of one or both mitral leaflets into the left atrium. Although mostly a benign cardiac condition, a subgroup of patients develop severe ventricular arrhythmias that is a significant cause of sudden cardiac death in young adults [1-4]. Arrhythmic MVP is defined as the presence of mitral valve prolapse with or without mitral annulus disjunction (MAD) combined with frequent ventricular ectopy, complex ectopy or sustained ventricular arrhythmia in the absence of another well-defined arrhythmic substrate[5,9,16]. In these patients, ventricular arrhythmias most commonly originate from the mitral annulus, papillary muscles and outflow tracts [5-8]. Several risk markers have been proposed, but clinical risk stratification remains challenging. Ventricular arrhythmias in patients with arrhythmic mitral valve prolapse are associated with excess long-term mortality[9].

There is no established medical therapy to suppress ventricular arrhythmias and relieve arrhythmic symptoms in these patients, and conventional beta blocker therapy is often unsuccessful for both[8,9]. Invasive catheter ablation can suppress ventricular arrhythmias, and thus relieve symptoms, in a subset of patients. However, many patients have multifocal ventricular ectopy, often originating from deep in the myocardium or papillary muscles not easily accessible for catheter ablation. Furthermore, recurrence of ventricular arrhythmias is common despite initial successful catheter ablation procedures[8]. The only strategy to prevent sudden cardiac death for high-risk patients is to implant an ICD, but this approach does not provide any symptomatic relief. Thus, most patients with arrhythmic mitral valve prolapse lack effective treatment options with proven efficacy in clinical trials.

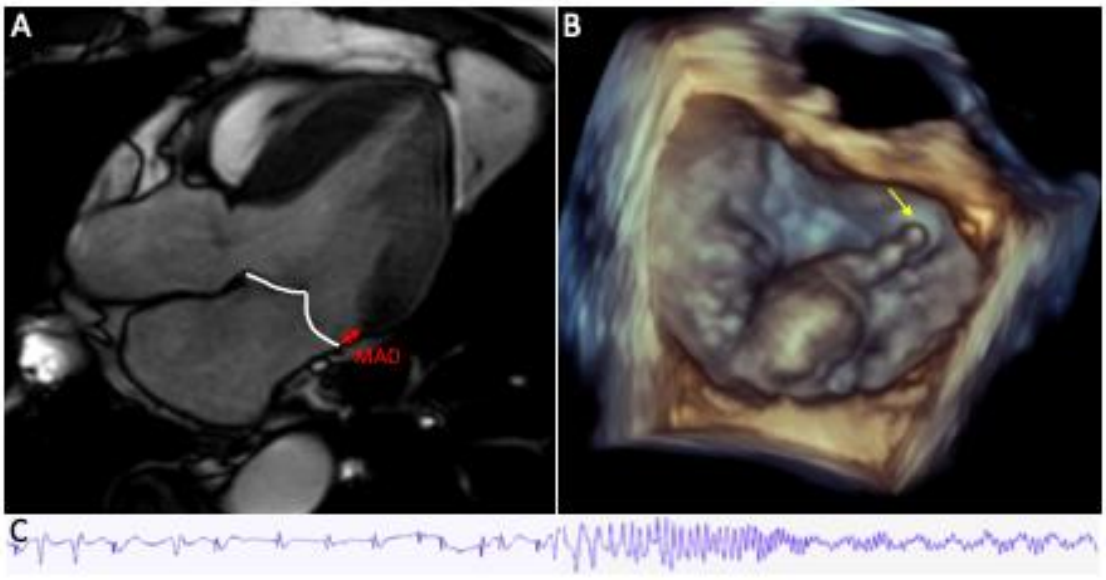

Figure 2. Ventricular fibrillation registered on a loop recorder in a study patient with MAD and MVP. A) Cardiac magnetic resonances showing mitral annulus disjunction (red). B) 3D echocardiographic image showing mitral valve prolapse. C) Ventricular fibrillation detected by implantable loop recorder (Reveal LINQ, Medtronic).

Flecainide is a class 1c antiarrhythmic drug with a potent sodium channel blocking effect frequently used in atrial tachyarrhythmias[10]. Flecainide was developed as treatment for ventricular arrhythmias[17], but its use subsided due to safety concerns when used in patients with acute myocardial infarction[18]. However, this knowledge stems from a patient population before modern revascularization strategies after myocardial infarction, and is extrapolated to patients with other structural heart disease. Lately, flecainide has been shown to be safe in patients with stable coronary artery disease[19,20]. Furthermore, flecainide reduce ventricular arrhythmias in patients with PVC-mediated cardiomyopathy[11], arrhythmogenic cardiomyopathy[12] and catecholaminergic polymorphic ventricular tachycardia[13] without short-term adverse effects.

Flecainide has not been studied in arrhythmic mitral valve prolapse patients, but a case series on patients with arrhythmic mitral valve prolapse proposed that flecainide in combination with beta blocker had better efficacy in suppressing ventricular arrhythmias than beta blocker alone without imparting increase in short-term arrhythmic risk[21]. Due to the lack of effective treatment options, the results from this limited case series could lead to a clinical utility of flecainide in these patients without robust evidence. Thus, a randomized, controlled trial is in order.

Previous studies have shown that patients with arrhythmic mitral valve prolapse have symptoms of palpitation, dyspnea, atypical chest pain and presyncope/syncope. However, whether these symptoms impact health-related quality of life is unknown. Furthermore, health-related quality of life has never before been systematically assessed in patients with arrhythmic mitral valve prolapse.

Short-form 36 questionnaire and Hospital Anxiety and Depression Scale (HADS) questionnaire are validated questionnaires for assessing general health-related quality of life in a wide variety of patient populations, assessing both physical and mental components[22,23]. Using these validated questionnaires makes it possible to compare health-related quality of life between arrhythmic mitral valve prolapse and other patient populations.

We aim to assess whether the combination of flecainide and beta blocker is superior to beta blocker therapy alone in suppressing ventricular arrhythmias and reduce self-reported symptoms in patients with arrhythmic mitral valve prolapse.

2.3 Benefit/Risk Assessment

There are certain potential risks associated with participation in the trial. All investigational products have potential adverse effects. Flecainide has previously been associated with increased mortality in patients after myocardial infarction[18]. Because of this, flecainide use is discouraged in the presence of ischemic and structural heart disease[10]. However, this knowledge stems from a study performed on a vastly different clinical entity than arrhythmic mitral valve prolapse. It is challenging to translate the harmful effects of flecainide previously observed in patients after acute myocardial infarction before modern revascularization, to patients with other structural heart diseases[24]. Recently, flecainide in combination with beta blocker has shown to reduce ventricular arrhythmias in both patients with PVC-mediated cardiomyopathy and arrhythmogenic cardiomyopathy, without concerns of safety[11,12]. Furthermore, preliminary data have suggested that flecainide reduced PVC burden and device-detected non-sustained ventricular tachycardias with no short-term adverse events in patients with arrhythmic mitral valve prolapse[21] . However, we cannot dismiss a potential proarrhythmic effect of flecainide in the study participants, which can occur due to reentry mechanisms in myocardial scars or by the QT prolonging effect of flecainide.

Metoprolol is a beta blocker and class II antiarrhythmic drug considered standard care in most cardiac diseases predisposing for ventricular arrhythmias[10], and metoprolol is associated with favorable outcome in heart failure with reduced ejection fraction[25]. Beta blockers are also considered standard care in arrhythmic mitral valve prolapse in the lack of head-to-head trials on different treatment approaches. However, metoprolol has certain potential adverse effects frequently leading to reduced compliance, possibly affecting the role of beta blockers in prevention of ventricular arrhythmias.

Prevalence of adverse events after implantable loop recorder (ILR) implantation is reported to be low[26], with a prevalence of infection at 1%[27]. It is plausible that infection risk and overall complication risk today is even lower, given the small size, easy insertion technique and fast procedure of the LINQ

II™. Anticoagulant and antiplatelet therapy represents increased risk of local hemorrhage, and such therapy will be dosage-adjusted or paused at the operating physician's discretion if clinically safe. Local hematomas are generally easily controlled and treated and pose no risk of major bleeding because of location of operative site. The added safety of continuous heart rhythm monitoring from an ILR in FLECAPRO weighs up for the minimal risk of implantation.

Potential benefits should also be considered. If the trial hypothesis proves to be correct, all participants will have access to superior treatment for half of the study duration. Importantly, today's standard of care treatment with beta blockers alone is ineffective, leaving these patients with high symptomatic arrhythmic burden and high risk of experiencing severe ventricular arrhythmias. Participants will have close contact with the outpatient clinic at Oslo University Hospital, Rikshospitalet and may consider it favorable to have closer follow-up than standard clinical care at a specialized center.

Overall, we consider participation in FLECAPRO to be of relatively low risk. The balance between potential risks, benefits and clinical implications seems to justify the investigation.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of flecainide and metoprolol, as well as the risk of loop recorder implantation, may be found in the Summary of Product Characteristics (SmPC) for flecainide and metoprolol and Investigational Directions for Use (IDFU) for LINQ II.

3.0 Objectives and Endpoints

3.1 Objective

The main goal of FLECAPRO is to evaluate the effect and safety of adding flecainide to standard beta blocker therapy to reduce burden of ventricular arrhythmias in patients with arrhythmic mitral valve prolapse.

3.2 Hypothesis

A flecainide-based strategy is superior to a beta blocker-based strategy to suppress ventricular arrhythmias in patients with arrhythmic mitral valve prolapse.

3.3 Primary Endpoint

The main objective of FLECAPRO is to assess whether the combination of flecainide and metoprolol can reduce the number of ventricular tachyarrhythmias without imposing worse short-term arrhythmic risk, compared to standard beta blocker therapy. Since the most feared adverse event is

ventricular tachycardia or ventricular fibrillation, this study question translates into a composite primary endpoint:

- Number of ventricular tachyarrhythmias over 12 months of treatment, sum of:
    - Ventricular fibrillation
    - Ventricular tachycardia (broad complex tachycardias with heart rate >140/min)

We will monitor for ventricular tachyarrhythmias using continuous heart rhythm monitoring with an implantable loop recorder. Ventricular fibrillation is an abnormal fast heart rhythm causing cardiac arrest. Ventricular tachycardia is traditionally defined as broad complex tachycardia for more than 3 consecutive beats with heart rate >100 beats per minute[28]. However, loop recorders are programmed to store tachycardias above a certain preprogrammed threshold, most commonly the estimated maximum heart rate of the patient (230 – age for LINQ II). This threshold is set to avoid recording of normal sinus tachycardia (e.g. during exercise). Thus, the definition of ventricular tachycardia for the primary endpoint in FLECAPRO will relate to the programmed detection zones of the loop recorders. We will program the ILRs for optimally detecting ventricular tachycardias, with automatic detection of rapid onset tachycardias with rate above 140 per minute (see section 7.3.2). The advantage for such a definition is that the primary endpoint will be more robust due to including only ventricular tachycardias faster than the traditional definition, and thus possibly more clinically relevant. However, a disadvantage will be that the definition is not based on traditional consensus. To detect possible ventricular tachycardias below the programmed detection zones, we will also perform Holter monitoring (see SoA), but ventricular tachycardias detected on Holter monitoring will not be included in the primary endpoint.

We expect some patients to have implanted a cardioverter defibrillator (ICD) prior to screening. In these patients, the primary endpoint will only be assessed by the implantable loop recorder and not the ICD itself. This is due to the difference in detection zones between loop recorder and ICD, and between different ICD manufacturers.

3.4 Secondary Endpoints

Secondary endpoints are categorized as key secondary endpoints (hierarchical testing only), secondary safety endpoints and exploratory secondary endpoints (all tested for hypothesis generation).

3.4.1 Key secondary endpoints (hierarchical)

- Burden of premature ventricular complexes, intention-to-treat, superiority

- Health-related quality of life (number of patients with ≥5-point increase in SF-36 overall summary score), intention-to-treat, superiority

- Number of severe ventricular tachycardias, intention-to-treat, superiority, sum of:

    - Non-sustained ventricular tachycardia with syncope

    - Sustained ventricular tachycardia (broad complex tachycardias with heart rate >140/min lasting for more than 30 seconds or requiring cardioversion)

    - Ventricular fibrillation

3.4.2 Secondary safety endpoints

- Safety composite, safety population, sum of:

    - The number of adverse events

        - Adverse reactions

    - The number of serious adverse events

        - Serious adverse reactions

    - Higher degree AV block (Mobitz type 2 or 3rd degree AV block)

3.4.3 Exploratory secondary endpoints

- Components of primary composite endpoint:

    - Ventricular tachycardia

    - Ventricular fibrillation

- Components of key secondary endpoints:

    - Burden of premature ventricular complexes

    - Improved health-related quality of life (number of patients with ≥5-point increase in SF-36 overall summary score)

    - Number of severe ventricular tachycardias

        - Non-sustained ventricular tachycardia with syncope

        - Sustained ventricular tachycardia

        - Ventricular fibrillation

- Left ventricular ejection fraction (change)

- N-terminal pro-B-type natriuretic peptide (change)

- NYHA class

- T-wave inversions (change)

- Degree of mitral regurgitation (change)

- Health-related quality of life as assess by the HADS questionnaire

- Per-protocol primary efficacy endpoint sensitivity analysis

- Intention-to-treat secondary safety endpoint sensitivity analysis

If other secondary endpoints become of interest during the study period, they will be highlighted as not pre-defined.

3.5 Corresponding Objectives and Endpoints

	Objective	**Endpoint measured at 13 and 26 months**
Primary	To assess whether flecainide and metoprolol can reduce number of ventricular tachyarrhythmias without imposing worse short-term arrhythmic risk	*Primary endpoint:* - Number of ventricular tachyarrhythmias (composite of ventricular tachycardia and ventricular fibrillation)
Secondary	To assess the efficacy of flecainide and metoprolol in reducing ventricular arrhythmias and arrhythmic symptoms compared to metoprolol alone	*Key secondary endpoints:* - Burden of premature ventricular complexes - Improved health-related quality of life assessed by SF-36 questionnaire - Number of severe ventricular tachycardias (composite of non-sustained ventricular tachycardia with syncope, sustained ventricular tachycardia and ventricular fibrillation)
Safety	To assess the safety of flecainide and metoprolol compared to metoprolol alone	*Secondary safety endpoints:* - The number of adverse events - The number of serious adverse events - Higher degree AV block

Exploratory	To generate hypotheses of potential beneficial effects of flecainide and metoprolol compared to metoprolol alone in patients with arrhythmic mitral valve prolapse	*Exploratory secondary endpoints:*
		- Components of primary composite endpoint:
		  - Ventricular tachycardia
		  - Ventricular fibrillation
		- Components of key secondary endpoints:
		  - Burden of premature ventricular complexes
		  - Improved health-related quality of life assessed by SF-36 questionnaire
		  - Number of severe ventricular tachycardias:

		- Non-sustained ventricular tachycardia with syncope - Sustained ventricular tachycardia - Ventricular fibrillation - Left ventricular ejection fraction (change) - N-terminal pro-B-type natriuretic peptide (change) - NYHA class - Health-related quality of life as assess by the HADS questionnaire - Per-protocol primary efficacy endpoint sensitivity analysis - Intention-to-treat primary safety endpoint sensitivity analysis

4.0 Study Design

4.1 Overall Design

We will design the study as a prospective randomized open-label blinded-endpoint (PROBE) crossover trial. Participants will receive equal time-periods of 12 months with the study intervention (flecainide + metoprolol) and with control (metoprolol) in a 1:1 randomized order. Randomization will be performed after inclusion and at the time of ILR implantation. Participants will have a run-in/washout period of 1 month at the beginning of the two treatment periods. The total duration of participation in FLECAPRO is 26 months (2 periods of 1 month run-in/washout and 12 months of fixed dose).

For assessing the primary endpoint and safety, every patient will have continuous heart rhythm monitoring using an implantable loop recorder (ILR). The device will be implanted prior to randomization and initiation of study intervention. Patients with a prior cardiac device (pacemaker or ICD) will also receive an implantable loop recorder. Additionally, at screening and after 1, 6 and 12 months of both treatment periods, we will perform 24-hour ambulatory Holter monitoring, which is a portable device for continuous recording the heart rhythm during 24 hours. This will detect ventricular tachycardias below the programmed detection zone of the implantable loop recorder and quantify premature ventricular complexes.

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

Note: “Enrolled” means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened

for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

4.1.1 Study Duration

Participants will be treated with the intervention arm for 13 months and the control arm for 13 months. Each arm will have a run-in/washout period of 1 month.

4.1.2 Estimated Study Period

The outpatient clinic at Oslo University Hospital, Rikshospitalet treats many patients with arrhythmic mitral valve prolapse per year, and this number is steadily increasing. We retrospectively assessed study inclusion and exclusion criteria in the patient population of 3 months from October to December 2021 at the outpatient Clinic of Oslo University Hospital, Rikshospitalet, prior to performing these calculations and observed that 13 of 18 patients (72%) would have been eligible for inclusion. Additionally, we will screen patients with arrhythmic mitral valve prolapse admitted to Department of Cardiology for symptomatic ventricular arrhythmias. This implies a realistic eligibility of at least 55 patients per year, meaning that inclusion will be completed within 1 year after study start. With study start on January 4th 2023, we estimate complete recruitment by January 31st 2026, and last subject last visit by March 31st 2028.

4.2 Scientific Rationale for Study Design

The crossover design of FLECAPRO was chosen because the number of arrhythmic mitral valve prolapse patients eligible for such a study is small, making recruitment difficult for a standard randomized parallel group trial design. Additionally, the added safety monitoring with using ILRs in FLECAPRO leads to an economic and an ethical limitation of group size when other study designs with fewer patients are suited. Furthermore, a crossover design reduces the random skewed distribution of known and unknown variables between randomized groups.

The traditional trial design to minimize bias is the double blind placebo design. Placebo control was discussed during the planning of FLECAPRO. Firstly, proper patient blinding provides only a small benefit and will include manufacturing several drug combinations of flecainide and metoprolol, which is non-feasible practically and economically. Secondly, measuring flecainide serum concentrations at each visit will lead to unblinding of trial personnel. Measuring flecainide serum concentration is necessary in patients with arrhythmic events during the course of FLECAPRO to avoid overdosing and potential risk of proarrhythmias. Thirdly, the aim of FLECAPRO is to assess the efficacy of the treatment strategy rather than a head-to-head comparison between flecainide and metoprolol. The randomization process will reduce potential bias. Fourthly, the primary endpoint and key secondary endpoints, except quality-of-life assessment, are not likely influenced by the lack

of patient blinding. Furthermore, adequately blinded adjudication of the pivotal study endpoints can be achieved using the PROBE-design.

Metoprolol is considered the standard of care for patients with arrhythmic mitral valve prolapse and is thus a natural control. Because participants of FLECAPRO is considered high risk of ventricular arrhythmias, having a control without active compound cannot be justified ethically.

4.2.1 Patient Input into Design

A panel of users has been recruited via the outpatient clinic at Oslo University Hospital, Rikshospitalet. The user panel has participated in the trial planning. They have emphasized the importance of close follow-up and that information regarding enrollment in the study should be duplicated in the patient's electronic medical record and provided to the primary care physician and local hospital.

Furthermore, they have been consulted in establishing the rate of physical visits and Holter monitoring during follow-up, which is aimed at creating a compromise between good safety monitoring and individual intrusiveness. Lastly, they have been consulted in establishing the hierarchical order of key secondary endpoints.

Further user representation is planned at the following time-points (all approximate):

- October 2022
    - Start-up meeting prior to enrollment of first patient, discussion of approved study proceedings and incorporations of previous feedback. Discussions of whether additional alterations should be made before inclusion starts.
- May 2023
    - Early evaluation meeting after 6 months of inclusion experience and early follow-up. Discussion of challenges.
- November 2023, 2024
    - Yearly evaluations and discussions of progression and interaction with trial participants. Considerations of remarks to be made in the yearly rapport.

The user panel will receive re-imbursement for any expenses and will receive a non-monetary gratification for their efforts.

4.3 Justification for Dose

4.3.1 Flecainide + Metoprolol SR (Intervention):

Flecainide will be initiated in as immediate-release formulation at a dose of 50 mg BID, and increased to the maximum tolerable dose, with a dosage target of 100 mg BID. The first dose of flecainide (100

mg) will be initiated in-hospital with 12-lead ECG taken after 3 hours (at maximum plasma concentration). Then, the participant will continue with 50 mg BID from the next day. The decision to proceed to the next dose level (either an increase or decrease) will be made by the Study Team and the investigator based on safety, tolerability, ECG changes and measurements of plasma concentration of flecainide. The maximum daily dose of flecainide will not exceed 300 mg. Whether Flecainide will be initiated on an inpatient or outpatient basis, will be decided on a case-by-case basis based on clinical features and current recommendations.

Study Team or investigator can change the immediate-release formulation to controlled-release form QD in case participants are stable on Flecainide 100 mg BID and have one of the following; (1) reduced compliance to twice a day dosing of flecainide, (2) preference for once a day dosing or (3) large fluctuations in plasma concentrations.

Flecainide has the potential to convert atrial fibrillation to atrial flutter with slow atrial rate leading to 1:1 atrioventricular conduction with high ventricular rate. This phenomenon can be prevented by concomitant therapy with negative dromotropic agents (e.g. beta blockers, verapamil, diltiazem or digoxin). A few of our patients will have moderate mitral regurgitation, with the potential of developing atrial fibrillation. Because of this safety concern, the study intervention will include a negative dromotropic agent. To avoid different medications with unknown efficacy, we will only permit metoprolol sustained release as this dromotropic agent, with a targeted daily dose identical to the control arm (see section 4.4.2 below), but will not exceed 200 mg. The starting dosage will be decided by the Study Team and investigator based on individual patient's prior dose, tolerability and safety. The decision to proceed to the next dose level will be based on safety and tolerability.

4.3.2 Metoprolol SR (Control)

The Study Team and investigator will decide the starting dosage of metoprolol taking into consideration prior beta blocker use and concomitant medications. The decision to proceed to the next dose level (either increase or decrease) will be based on safety and tolerability. Whether metoprolol sustained release will be dosed QD or BID, will be up to the investigator and patient preference. The maximum daily dose of metoprolol will not exceed 200 mg.

4.4 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if he/she has completed all phases of the study including last visit or the last scheduled procedure shown in the SoA.

5.0 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be 18 years of age or older at the time of signing the informed consent

Mitral valve prolapse

2. Participants must have mitral valve prolapse evident by echocardiography or cardiac magnetic resonance imaging, defined as:
    a. More than or equal to 2 mm atrial displacement of any part of the mitral leaflets (mitral valve prolapse)

Ventricular arrhythmias

3. Participants must have ventricular arrhythmias, defined as at least one of the following:
    a. Premature ventricular complex burden ≥3% per 24-hours by Holter monitoring
    b. Premature ventricular complex burden ≥1% per 24-hours if multifocal or occurring in bi-/trigemini and/or couplets by Holter monitoring
    c. Sustained or non-sustained ventricular tachycardia
    d. Aborted cardiac arrest
4. Participants must have a clinical indication for antiarrhythmic treatment due to ventricular arrhythmias

Informed consent

5. Participants must be capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF)

For women of childbearing potential

6. Participants must accede to mandatory use of a contraceptive method for the duration of the trial and until 3 days after discontinuation of study medication.

Rescreening will be allowed if a participant at a later time point develops ventricular arrhythmias as per definition stated above. Participants will only be eligible for rescreening two times.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Contraindication to Study Medications

1. Strict contraindication to flecainide or metoprolol use

Medical Conditions

2. Heart failure (signs or symptoms, elevated NT-proBNP) according to ICD10
3. Abnormal liver or kidney function (AST/ALT three times upper normal, eGRF <60)
4. Prior myocardial infarction or ischemic heart disease
5. Ion channelopathy, including Brugada syndrome and long QT syndrome according to ICD10 and ECG
6. Genetic cardiomyopathy (hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy, dilated cardiomyopathy, including genotype positive phenotype negative individuals) according to ICD10
7. Atrial flutter or permanent atrial fibrillation according to ICD10 and ECG
8. Sinus node dysfunction according to ICD10 and ECG
9. Ongoing electrolyte disorders
10. More than moderate valvular disease according to international guidelines[29]

Electrocardiogram

11. Pre-excitation
12. Any degree of AV-block, except due to enhanced vagal tone (e.g. Wencheback-block at night in young athletes or 1st degree AV block that disappears during exercise)
13. Bundle branch block (QRS duration >120 ms) or intraventricular conduction defect with QRS >120 ms

Prior/Concomitant Therapy

14. Prior flecainide therapy
15. Concomitant use of the following medications:
    a. CYP2D6 inhibitors/inducers
    b. Class I, III or IV antiarrhythmic drugs
    c. Clozapine, quinidine, cimetidine, bupropion
    d. Monoaminoxydase (MAO) inhibitors

Women of Childbearing Potential

16. Pregnancy
17. Not willing to use a mandatory contraceptive method for the duration of the trial

5.2.1 Coronary Artery Disease/Anomaly Assessment

Because of the results of the CAST trial showing increased mortality in patients treated with flecainide after myocardial infarction, we will exclude coronary artery disease in the participants of FLECAPRO. Most participants recruited will already have excluded coronary artery disease, as this condition is an important differential diagnosis of arrhythmic mitral valve prolapse. However, we will assess all patients for symptoms of coronary artery disease at screening. Participants not already assessed by coronary angiography within the last two years prior to screening will be evaluated with CT or invasive coronary angiography at baseline if symptomatic.

We will not perform coronary angiography in patients without symptoms of coronary artery disease, as this will expose participants to potential unnecessary and dangerous invasive procedures. A screening CT coronary angiography has been discussed in the planning of FLECAPRO. However, uncertain findings or uncertain degree of obstructive coronary artery disease will need further assessment by invasive coronary angiography with potential for deleterious events in asymptomatic individuals.

5.3 Lifestyle Considerations

Participants should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, from the day of starting the study intervention until after the final dose. There are no restrictions on ingesting caffeine- or xanthine-containing products (coffee, tea, cola drinks and chocolate), or use of tobacco products.

5.4 Screening Failures

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) due to not fulfilling inclusion criteria may be rescreened. A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 3 months from the previous ICF signature date.

6.0 Study Interventions and Concomitant Therapy

Study intervention is defined as any investigational interventions intended to be administered to a study participant according to the protocol. All participants enrolled in FLECAPRO will be treated with both the intervention arm (flecainide and metoprolol) and control arm (metoprolol), and all participants enrolled will be have an ILR implanted.

6.1 Study Interventions Administered

Each study period will start with a run-in/washout period of 1 month. The first dose of flecainide will be 100 mg initiated in-hospital with 12-lead ECG taken 3 hours after intake (at maximum plasma concentration). Then the participant will continue with 50 mg BID from the next day. Flecainide dosage will be initiated at 50 mg BID and evaluated for increasing dose after 7 days to a maximum of 300 mg daily dose.

The flecainide dosage will be kept unchanged during the course of the treatment period, or according to plasma measurements and development of AEs.

Metoprolol will be initiated at a dosage that takes into account prior beta blocker use, and will be evaluated for increasing dose after 7 days to the maximum tolerated dose. Dosage will be kept at maximum tolerated dose during both the intervention arm and control arm.

Table 1. Study Interventions Administered

Intervention Name	Flecainide	Metoprolol
Type	Drug	Drug
Formulation	Tablets (immediate-release) Capsules (controlled-release)	Tablets
Unit Dose Strength(s)	100 mg (immediate-release) 200 mg (controlled-release)	200 mg
Targeted dose	200 mg daily (100 mg BID immediate-release or 200 mg QD controlled release)	200 mg QD
Route of Administration	Oral	Oral
Use	Experimental treatment strategy	Background intervention
IMP or AxMP	Investigational medicinal product (IMP)	Investigational medicinal product (IMP)
Sourcing	Shelf product	Shelf product
Packaging and Labeling	Study intervention will be provided in original package. Each package will be labeled as required per country requirement.	Study intervention will be provided in original package. Each package will be labeled as required per country requirement.
Current/Former Names or Aliases	Immediate-release: Flecainide, Tambocor	Metoprolol, Selo-Zok, Bloxazoc

	Controlled-release: Tambocor Retard	

Table 2. Study Arms

Arm Title	Flecainide and Metoprolol	Metoprolol Alone
Arm Type	Experimental	Active Comparator
Arm Description	Participants will receive Flecainide 50 mg BID, with a dosage target of 100 mg BID. The maximum daily dose of flecainide will not exceed 300 mg. The first dose of flecainide will be 100 mg and initiated in-hospital with 12-lead ECG taken after 3 hours (at maximum plasma concentration). The participant will continue with 50 mg BID from the next day. Participants will receive a dosage of Metoprolol taking into consideration prior beta blocker use and concomitant medications. The maximum daily dose of metoprolol will not exceed 200 mg. Within the run-in period, the dosage of both Flecainide and Metoprolol will be increased to the maximum tolerable dose. The Study Team can change the immediate-release formulation of Flecainide to controlled-release at the same daily dose of flecainide (see section 4.3). Whether metoprolol sustained release will be dosed QD or BID, will be up to the investigator and patient preference.	Participants will receive a dosage of Metoprolol taking into consideration prior beta blocker use and concomitant medications. Within the run-in period, the dosage will be increase to the maximum tolerable dose. Whether metoprolol sustained release will be dosed QD or BID, will be up to the investigator and patient preference. The maximum daily dose of metoprolol will not exceed 200 mg.
Associated Intervention Labels	Flecainide immediate-release: Flecainide, Tambocor Flecainide controlled-release: Tambocor Retard Metoprolol: Metoprolol, Selo-Zok, Bloxazoc	Metoprolol, Selo-Zok, Bloxazoc

6.1.1 Flecainide

Flecainide is a class Ic antiarrhythmic drug that was approved by the Food and Drug Administration in 1984 for the treatment of symptomatic sustained ventricular tachycardia, with a 90% efficacy and without significant adverse events[17,30]. The main mechanism of flecainide is blocking myocardial sodium channels leading to a reduction in ventricular myocardium conduction velocity. In addition, flecainide has an inhibitory action on potassium channels, which increases the duration of the action potential and the effective refractory period in the myocardium. Because of these pharmacodynamics effects, flecainide prolongs the PR (17-29%) and widens the QRS complex (11-27%), but the effect of flecainide on JT-interval is negligible. The third mechanism of action is the blocking of ryanodine receptor 2 calcium channels, making it a good treatment option for patients with catecholaminergic polymorphic ventricular tachycardia[13].

Currently, flecainide is mainly used for pharmacological conversion in rhythm control strategies in patients with atrial tachyarrhythmias[10]. The Cardiac Arrhythmia Suppression Trial (CAST) investigated the efficacy of class Ic antiarrhythmic therapy on morbidity and mortality in patients with reduced ejection fraction and frequent premature ventricular complexes after myocardial infarction[18]. This study recorded significantly higher mortality among patients treated with IC antiarrhythmic drugs compared to placebo and the study was prematurely dismissed. The CAST study provided a major revision of the role of flecainide, which is now recommended in selected patients with preserved systolic function and without ischemic heart disease. However, the CAST trial was performed prior to modern myocardial infarction treatment, and flecainide use in stable coronary artery disease has recently been shown to be safe[19,20]. In addition, current guidelines extended the CAST findings to non-ischemic structural heart disease despite limited evidence[10]. Thus, we have seen a fall in employment of class IC antiarrhythmic drugs in favor of class III antiarrhythmic drugs, exposing patients to the numerous adverse reactions and toxicities of the latter drugs, in the absence of robust evidence.

On the other hand, recent studies demonstrated safety and efficacy of flecainide in patients with PVC-induced cardiomyopathy[11] and arrhythmogenic cardiomyopathy[12]. A randomized placebo-controlled crossover trial on flecainide in patients with arrhythmogenic cardiomyopathy is ongoing (ClinicalTrials.gov Identifier: NCT03685149). Furthermore, guidelines state a class I recommendation level of evidence C for treatment with class IC antiarrhythmic drugs in patients with symptomatic ventricular tachycardia originating from the mitral annulus, outflow tracts, papillary muscles or left ventricle in the absence of structural heart disease[10]. These areas of arrhythmia origins are similar to areas where ventricular arrhythmias originate in patients with arrhythmic mitral valve prolapse[1,2,6,7].

According to the Summary of Product Characteristics (SmPC) for flecainide, measuring plasma levels is recommended in case of reduced heart function, high-dose treatment or long-term treatment. We will be measuring plasma levels at each study visit (after 1, 6 and 12 months) during both study arms where the therapeutic range will be 200-1000 ng/ml (0.4-2.0 µmol/L).

The medication will be managed in agreement with the SmPC for flecainide. All reference safety information will be based on the SmPC for flecainide. A detailed description of the chemistry, pharmacology, efficacy, and safety of flecainide is provided in the SmPC for flecainide.

6.1.2 Metoprolol

Metoprolol is a beta-blocker and class II antiarrhythmic drug considered standard care in most cardiac diseases predisposing for ventricular arrhythmias[10], and is associated with decreased mortality in patients with heart failure with reduced ejection fraction[25]. Beta-blockers are also considered standard care in arrhythmic mitral valve prolapse in lack of trials on other treatment strategies. However, metoprolol has certain potential adverse effects frequently leading to reduced compliance, especially in younger patients, possibly affecting the role of beta-blockers in prevention of ventricular arrhythmias.

The medication will be managed in agreement with the SmPC for metoprolol. All reference safety information will be based on the SmPC for metoprolol. A detailed description of the chemistry, pharmacology, efficacy, and safety of metoprolol is provided in the SmPC for metoprolol.

6.2 Preparation, Handling, Storage, and Accountability

The investigators will prescribe the investigational products and local pharmacies will supply the investigational products as per clinical practice. This will ensure than only participants enrolled in the study receive study interventions. Handling, storage, reconciliation, accountability and record maintenance of the investigational products will be handled as by regulatory requirements. All batch numbers are systematically stored in the electronic patient journal (Kjernejournal). This will enable secure identification of batches involved in any adverse events.

6.3 Assignment to Study Intervention

All participants will be assigned to a randomized sequence of study arms executed on the online, password protected platform designed for study purposes (Viedoc®) once eligibility has been confirmed, informed consent has been signed and loop recorder has been successfully implanted.

Due to small sample size, the allocation to treatment using permuted block randomization could lead to imbalance in prognostic factors in the two groups, especially in terms of arrhythmic risk profile. This could lead to problems when interpreting the results of the study. As a measure to prevent such

allocation bias and ensure balance of baseline prognostic factors between groups, we will use a computerized randomization procedure with probabilistic minimization with 80% balanced allocation (in a 1:1 ratio for the sequencing of the study arms). The prognostic factors we include are gender, age (<40 and ≥40years), sustained ventricular tachycardia or aborted cardiac arrest, NSVT, presence of late gadolinium enhancement, presence of mitral annular disjunction, bileaflet mitral valve prolapse and ECG T-wave inversions. All of the prognostic factors, including female gender and younger age, are linked to increased risk of ventricular arrhythmias in observational studies.

After randomization, the study personnel will enter a statement to the patient's electronic medical record declaring the allocation, treatment sequence and duration. This statement will be distributed to other physicians caring for the patients and will include a recommendation to only alter the study medication if it is critically important, documenting reasons and time of changes of study's medications.

If more than 4 weeks have passed since the screening visit, the physical exam should be repeated, vital signs recorded anew, and blood samples should be repeated.

6.4 Blinding

It is vital for an open-label blinded-endpoint randomized trial to maintain proper blinding to uphold scientific integrity of data. Therefore, careful logistic arrangements will be made to avoid bias in the endpoint adjudication. Only the investigators assessing the outcome measures will be actively blinded for the allocation.

6.4.1 Implantable loop recorder

Events recorded by the implantable loop recorder stored in the Carelink system will be de-identified and coded with the patient study ID to ensure that the reader will not come across details of the treatment. A second expert reader will be contacted by a principal investigator if the primary reader finds:

- Blinding is compromised. The primary reader ensures proper blinding and forwards the exam for blinded analysis.
- There is uncertainty in the adjudication. Consensus will be achieved.

6.4.2 Holter monitoring

Holter monitoring data will be de-identified and coded with the patient study ID to ensure that the reader will not come across details of the treatment. A second expert reader will be contacted by a principal investigator if the primary reader finds:

- Blinding is compromised. The primary reader ensures proper blinding and forwards the exam for blinded analysis.
- There is uncertainty in the adjudication. Consensus will be achieved.

6.5 Study Intervention Compliance

Participant compliance to the investigational products will be self-reported by asking the participant to report their compliance as either full, partial or low. Full compliance is defined as taking the treatment as prescribed, partial compliance is less than full but more than 70% compliance to prescribed treatment, and low compliance is less than 70% compliant. Deviation from the prescribed dosage regiment will be recorded. The compliance of flecainide use will also be reflected in the plasma concentration measurements. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded. The data will be reported with the trial results. The batch numbers of used study medication will be found in the electronic patient journal (Kjernejournal).

6.6 Dose Modification

After the run-in period, the dosage of study intervention will be held constant throughout the treatment periods. However, if a dose reduction is necessary, flecainide will be reduced with 50 mg daily and metoprolol with 50 mg daily. The dose reduction can be greater if the medical monitor or Data Monitoring Committee see it necessary due to safety concerns.

6.7 Continued Access to Study Intervention after the End of the Study

Participants can continue with any of the study arms after end of the study. The combination of flecainide and metoprolol can only be continued if the participant is under continuous heart rhythm monitoring with ICD or ILR.

6.8 Treatment of Overdose

Overdose will be defined and managed according to the SmPC for flecainide and metoprolol. In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be discontinued or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until flecainide is within the treatment range defined in section 6.1.1.
- Document the quantity of the excess dose as well as the duration of the overdose.
- Report the overdose as a protocol deviation.

6.9 Prior and Concomitant Medication

Use of concomitant medication is permitted if not a trial exclusion criterion (i.e. not a known inhibitor or inducer of CYP2D6, MAO-inhibitors, or class I, III or IV antiarrhythmic drugs other than flecainide). Starting these medications during the trial period is not permitted. For other and permitted concomitant medication, potential interactions and notions of care from the SmPC shall be considered and noted at inclusion.

There might be cases where other antiarrhythmic drugs, especially amiodarone (class III antiarrhythmic drug), will be administered due to ventricular tachyarrhythmias occurring in FLECAPRO participants. It is important to stress the fact that no antiarrhythmic drug, even amiodarone, has been studied in patients with arrhythmic mitral valve prolapse. In case not permitted drugs has be to administered, patients will be discontinued from treatment in FLECAPRO.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Paracetamol, at doses of 2 grams/day, is permitted for use and time during the study. Other concomitant medications may be considered on a case-by-base basis by the investigator in consultation with the medical monitor, if required.

7.0 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

The study participants may discontinue study drug treatment at any time according to their preferences. The investigator may also advise study drug discontinuation in case of:

- Starting other anti-arrhythmic drug (e.g. amiodarone, sotalol or carvedilol).
- Diagnosis of coronary artery disease, including unstable angina or myocardial infarction.
- Hospitalization due to ventricular arrhythmias, cardiac arrest, symptomatic bradycardia or new onset of heart failure.
- QRS prolongation >25% compared to baseline QRS duration.
- Contraindication to the continued use of flecainide or metoprolol arises.
- AEs/SAEs

Discontinuation and the reason why must be documented in the eCRF as well as in the hospital record. Efforts will be made to ensure that adherence to the study protocol is kept up even though

the patient no longer takes the study drug. All available data will be used, unless the patient specifically disagrees to let the investigator use his or her data.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient are:

- Voluntary discontinuation: participants are free to discontinue their participation in the study at any point in time, without prejudice to further treatment.
- Patient lost to follow-up

Patient withdrawal and the reason must be documented in the eCRF as well as in hospital records. If possible, a final assessment should be obtained (Early Termination Visit, see SoA). The investigator is obliged to follow up any significant adverse events until the outcome either is recovered or resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequela, fatal or unknown. The implantable loop recorder could be removed after agreement with the study participant.

7.3 Trial Discontinuation

The whole trial may be discontinued at the discretion of the Principal Investigator/Sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients

The Sponsor and Principal Investigator will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial, along with the reasons for such action. If the study is terminated early because of safety concerns, the Competent Authorities and Ethics Committees will be informed within 15 days.

7.4 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit

schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8.0 Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g. laboratory analyses) and obtained before signing of the ICF may be utilized for screening purposes provided the procedures met the protocol-specified criteria.

In the event of a significant study-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

Repeat or unscheduled blood samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and Baseline Procedures

8.1.1 Informed Consent

Voluntary, written informed consent must have been obtained for each subject before any study specific procedure is initiated. At this time, the patient will be registered in the electronic Case Report Form (eCRF), and a unique identifier will be assigned.

8.1.2 Physical Examination

A physical examination (including examination of heart, lungs, abdomen, neck and assessment of peripheral circulation and edema) must be performed; vital signs (blood pressure and heart rate, and height and weight) will be recorded.

8.1.3 Vital Signs

Vital signs will be measured after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

8.1.4 Medical History

A medical history will be obtained, along with age, gender, NYHA functional status, risk factors (hypertension, smoking and diabetes mellitus) and concomitant disease must be recorded. Additionally, every participant will undergo clinical evaluation for assessing pre-test probability of coronary artery disease.

8.1.5 Concomitant Medication

All concomitant medication used by the participant within 28 days of the start of treatment must be recorded in the eCRF by generic name and dose.

8.1.6 Laboratory Analyses

Non-fasting blood samples will be obtained at maximum 9 different time points (see SoA). Six blood samples (24 ml) will be taken 7 times. Blood samples for biobanking will be taken 3 times (4 samples, 22 ml) and be appropriately labelled and stored in a trial specific biobank for the duration of the trial and later analyzed for vasoactive peptides such as ST2 and markers of fibrosis. Flecainide serum concentration will be assessed 8 times (1 sample, 4 ml). The maximum number of blood samples on one single occasion will be 10 (46 ml total volume). Samples will be labeled and marked with initials and date of birth of the participant. A dedicated study nurse, as well as the respective analyzing units, will have access to the samples.

The baseline blood samples will be part of routine health care, but the additional blood samples obtained will be trial specific. Standard blood samples will be used to determine: Hemoglobin, white blood cell count, platelet count, serum potassium, serum sodium, glucose, glycosylated hemoglobin (HbA1c), creatinine, eGFR, ALT, AST, bilirubin, albumin, INR, NT-proBNP and troponin T.

All samples, except flecainide serum concentration, will be analysed within Oslo University Hospital. Flecainide serum concentration will be analysed at St. Olav's Hospital, Trondheim, Norway. Samples sent to St. Olav's Hospital will be destroyed after the analyses are completed.

8.1.7 Transthoracic Echocardiography

Echocardiography is the most widely used imaging method in cardiology for assessing valvular and myocardial function, and predict outcome. The echocardiographic study will be performed on a Vivid E9 or higher (GE Healthcare, Horten, Norway). Data will be analyzed with EchoPac (GE Healthcare). Measurements of cardiac cavities will be performed using M-mode and 2D modalities for internal linear dimensions and volumes. Ejection fraction is calculated by using Simpson`s modified biplane method utilizing endocardial contours in the apical 4-chamber and 2-chamber view. Assessment of heart valves will be performed using color Doppler, and pulsed and continuous wave Doppler. Diastolic function will be evaluated by transmitral pulsed Doppler, tissue Doppler and left atrial volume assessment[31]. Tissue Doppler from the 4-chamber view will be recorded and e' will be calculated as the average from septal and lateral samplings [32]. Atrial volumes and areas will be averaged as the end-systolic area measured from apical four-chamber and apical two chamber views [32].

We will assess mitral annular disjunction (MAD) in end-systole, and measure the distance from the left atrial wall-valve leaflet junction to the top of the left ventricular wall [33-35]. We will assess the presence of MAD in both the parasternal long-axis view, and all apical long-axis views.

Myocardial strain measurements have been proven to be superior to 2D echo for assessing regional LV function[36]. Myocardial global longitudinal strain will be obtained by speckle tracking technique. Peak systolic strain by 2D speckle tracking echocardiography will be determined using a 16-segment left ventricular model recommended by the American Heart Association. Myocardial systolic strain will be studied to characterize regional myocardial function and timing in all study patients. The time to maximum shortening in each patient's 16 left ventricular segments will be calculated[37]. The standard deviation of these time measurements will be calculated as mechanical dispersion, reflecting contraction heterogeneity (Figure 3)[37].

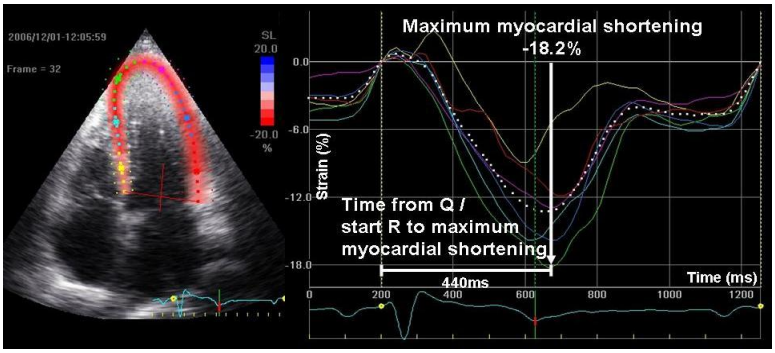

Figure 3: Strain curves in 4-chamber view after myocardial infarction. Maximum myocardial shortening in septal apical segment is indicated (white arrow) and time from ECG onset Q/onset R wave to maximum myocardial shortening (time line). Global strain: average value of maximum myocardial shortening in 16 left ventricular segments. Mechanical dispersion: Standard deviation of time interval from ECG onset Q/onset R wave to maximum myocardial shortening in 16 LV segments. (From Haugaa et al, J Am Coll Cardiol Imaging 2010).

8.1.8 Cardiac Magnetic Resonance Imaging

If not performed within the last 24 months prior to screening or if the participant has a pacemaker or an ICD, a comprehensive cardiac magnetic resonance imaging exam for study purposes must be performed prior to study drug administration and implantation of loop recorder.

Cardiac magnetic resonance (CMR) done as a part of FLECAPRO will be performed using 1,5 or 3 Tesla scanner (Magnetom Vision Plus or Magnetom Sonata; Siemens, Erlangen, Germany) and a phased array body coil. The right and left ventricle will be covered by axial and sagittal breath-hold T1 weighted turbo spin echo images, and by multiple short axis cine images using a breath-hold segmented balanced gradient echo sequence (fast imaging with steady-state free precession). Two-chamber and four-chamber cine acquisitions will be obtained. Intravenous gadolinium-based contrast agents will be used, as late gadolinium enhancement has become the reference standard for noninvasive assessment of myocardial fibrosis [38-40]. Post-processing analysis will be performed for calculation of myocardial function by ejection fraction, to assess extent and distribution of myocardial fibrosis, structural pathology in mitral valve apparatus and measurements of MAD distance. T1 mapping will be used according to current protocols. We will perform CMR according to Oslo University Hospital's own safety procedures in participants with cardiac electronic devices prior to inclusion.

In addition to CMR at baseline, we will perform CMR in 10 participants shortly after successful ILR implantation. This will be done in order to assess whether the ILR interferes with measurements of T1 times. We will also perform an additional CMR (after successful ILR removal) in participants randomized to receive the intervention arm as the last treatment period, in order to assess whether treatment with flecainide decrease markers of diffuse fibrosis.

8.2 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA.

8.2.1 Implantable Loop Recorder

All enrolled participants will receive an ILR. Implantable loop recorder (ILR) is a small cardiac monitoring device implanted subcutaneously in the left parasternal precordial region, with approximately 4.5 years of battery capacity for LINQ II. The unit continuously monitors heart rhythm, and will store selected ECGs in the device memory according to a pre-programmed algorithm and/or by patient activation of the device. ILRs have been used for many years and is part of the established toolbox for evaluating patients with suspected paroxysmal cardiac arrhythmias, syncope and ventricular arrhythmias [26,41-43] [28,44]. The ILR is superior to conventional 24 hours Holter monitoring for detecting paroxysmal cardiac arrhythmias [26,27,41-43] as it is common for arrhythmias to appear with

long time-intervals. The use of ILRs for detection of paroxysmal cardiac arrhythmias is rapidly increasing, much due to steadily decreasing size of device, development of easy and fast implantation procedures and high degree of safety [26,45].

Prevalence of adverse events after ILR implantation is reported to be low[26]. Possible side-effects or complications include device rejection phenomena (local tissue reaction), device migration, local infection and erosion of the skin[46]. Recent studies have reported low prevalence of infection at 1%[27]. It is plausible that infection risk and overall complication risk today is even lower, given the small size of device, easy insertion technique and fast procedure of the LINQ II™.
The ILRs implanted in FLECAPRO will be programmed towards primarily (but not exclusively) detecting ventricular arrhythmias. We will use the CE approved Medtronic LINQ II™ Insertable Cardiac Monitor. For specifications and device measures, see the Clinician Manual for LINQ II. The device can be interrogated remotely by the investigator via the mobile network or Wi-Fi. Patients will also be monitored remotely (Carelink™) without the need for physical visits to the outpatient clinic, with daily transmission of data. When the ILR battery is depleted, it will be explanted, usually about 4.5 years post-implantation. The LINQ II™ is fully magnetic resonance imaging conditional.

If consultations or interrogation of ILR reveals pathology in need of treatment or further investigation, this will be handled as in a normal clinical setting with proper patient information and referral to adequate investigations.

At study completion, we will review all stored events for ventricular arrhythmias using the Carelink™ system.

8.2.1.1 Implantation Procedure

Implantation procedure will follow instructions from Medtronic's Clinicians Manual. Skin is sterilized and patient prepared according to standard surgical procedures at Oslo University Hospital, Rikshospitalet. Local anesthetic is infiltrated in the area of interest, a small incision is made in the skin, and the device is inserted via a custom insertion tool (Figure 4). The incision is closed with surgical tape or 1-2 sutures. Normal procedure time including appliance of anesthetic is 10 minutes. Anticoagulant and antiplatelet therapy represents increased risk of local hemorrhage, and such treatment will be evaluated pre-operatively in concert with other risk factors for bleeding. Anticoagulant or antiplatelet medication will be dosage-adjusted or paused at the operating physician's discretion if clinically safe. Local hematomas are generally easily controlled and treated and pose no risk of major bleeding because of location of operative site.

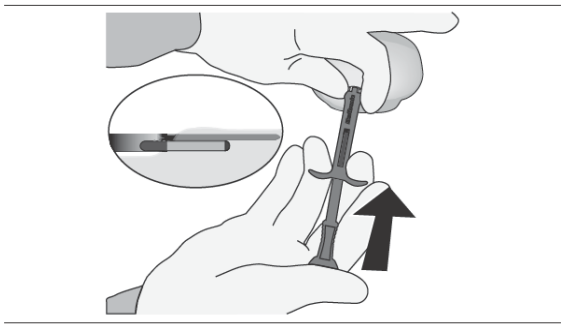

Figure 4. Insertion of implantable loop recorder. Medtronic LINQ II, Clinician's Manual.

8.2.1.2 LINQ II programming

The LINQ II will be programmed towards optimal detection of ventricular tachycardias, with tachycardia interval length of 430 ms (equals 140 bpm), tachycardia duration of 3 events and "Tachy: Require Rapid Onset" feature turned on. The "Tachy: Require Rapid Onset" function will be used to distinguish sinus tachycardia from ventricular tachycardias, as ventricular tachycardias exhibits a sudden rate increase, while sinus tachycardia is characterized by a gradual increase in rate. The "PVC Detection Enable" feature will be turned on. This feature is designed to detect single PVCs between two normal sinus beats and does not count any beats that are part of a couplet or triplet PVC series.

8.2.2 Holter Monitoring

Holter monitor is a portable device for continuous recording of ECG for 24 hours, and must be performed in all patients.

8.2.3 Health-related Quality of Life

Self-reported, health-related quality of life will be gauged with the SF-36 and HADS questionnaires at baseline and after each study arm, for a total of three times. This assessment will be done at home via mobile phone app directly connected to the eCFR (ViedocMe©), which is an integrated part of the eCRF (Viedoc©), 1 week before the end of treatment visit. Participants will receive a reminder via the app 3 days before the visit. The day before the visit, participants will be reminded via SMS. At the end of treatment visit, participants will be directly questioned if they filled the questionnaires remotely. If not, the participants will be able to get help with login, or fill out the questionnaires by hand. The quality-of-life assessments at baseline will be performed prior to randomization, and we will allow participants to complete the questionnaires assessments before study procedures are performed.

We will assess quality of life at baseline and after each study arm (see SoA) using validated questionnaires; Short Form 36 (SF-36) and Hospital Anxiety and Depression Scale (HADS) questionnaires. SF-36 is a self-reported measure of health and comprises of 36 questions covering

eight domains of health (limitations in physical and social activity, bodily pain, general mental health, limitation in usual role activities because of emotional and physical health problems, vitality and general health perceptions)[22]. These can also be combined to a "physical component summary" and "mental component summary". The SF-36 has been extensively validated and assessed[47]. Score range from 0 to 100 and higher scores indicate better health status, and a 5-point change over time can be interpreted as clinically relevant[47].

HADS measures anxiety and depression symptoms using 14 items on a 4-point scale[23]. The score range for both anxiety and depressive symptoms is 0-21 with higher scores indicating greater anxiety or depression. It has been proven to be reliable and valid in several populations[48].

8.3 Safety Assessments

Planned time points for all efficacy assessments are provided in the SoA.

8.3.1 Coronary Artery Disease Assessment

All patients will be thoroughly evaluated clinically at baseline for coronary artery disease or coronary anomalies (see Medical History above). If not performed within the last 2 years prior to screening, we will perform a CT or invasive coronary angiography according to guidelines in force[49].

8.3.2 Visits and Telephone Contact

We will conduct a physical visit to the study site at screening and after 1, 6 and 12 months during both treatment arms (see SoA). At these visits, we will perform 24-hour Holter monitoring and ECG. We will also review any signs of AE and SAE, assess compliance to study drug and measure plasma levels of flecainide.

During the course of the study, participants will be able to contact our study nurse for questions. We will also contact patients by telephone if we detect ventricular tachycardia on the remote Carelink™ system to assess symptoms of the event (if any).

8.3.4 Electrocardiogram

12-lead ECG will be obtained as outlined in the SoA (see Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals.

8.3.5 Exercise ECG

Exercise ECG will be obtained as outlined in the SoA (see Section 1.2), which is an ECG that is recorded while participants are cycling on an exercise bike.

8.3.6 Pregnancy Testing

Serum pregnancy testing will only be performed in WOCBP and at time points specified in the SoA. In addition, urine pregnancy tests will be provided free of charge to be used during the course of FLECAPRO.

8.4 End of Treatment Visits

An end of treatment visit will be conducted at the end of each treatment period. At this visit, we will assess compliance to study drug, perform ECG and physical examination, review any signs of AE and SAE, and perform a transthoracic echocardiography and exercise ECG.

8.5 Clinical Events

8.5.1 Ventricular Fibrillation

Ventricular fibrillation is an ultrafast and disorganized heart rhythm leading to abrupt loss of heart function and breathing (cardiac arrest). The implantable loop recorders will automatically detect and record such an event with exact time and date (Figure 5). Ventricular fibrillation will be defined (as per ECG) as:

- Chaotic irregular deflections of varying amplitude.
- No identifiable P waves, QRS complexes or T waves.
- Rate 150 to 500 per minute.
- Amplitude decreases with duration.

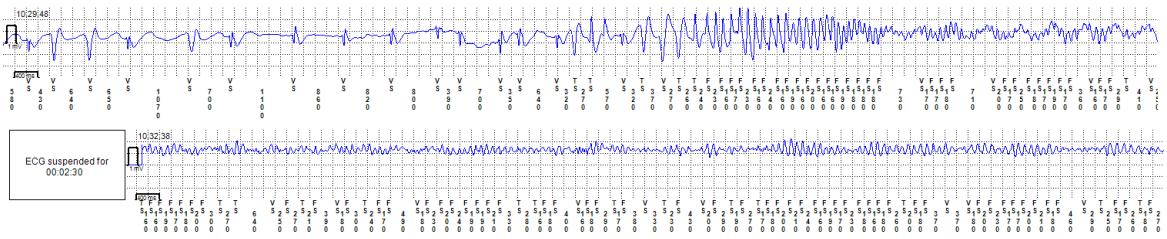

Figure 5. Ventricular fibrillation recorded by an implantable loop recorder in a patient with arrhythmic mitral valve prolapse.

8.5.2 Ventricular Tachycardia

The number of ventricular tachycardias will be assessed by implantable loop recorder (figure 6), electrocardiogram (ECG), Holter monitoring and stress ECG, and is defined as following:

- Three or more consecutive ventricular beats (QRS duration >120 ms) with heart rate > 100 beats/min.

Ventricular tachycardia outcome definition:

- Sustained ventricular tachycardia: lasting >30 seconds or terminated earlier due to hemodynamic instability.
- Non-sustained ventricular tachycardia with syncope: lasting <30 seconds, but leads to syncope (patient reported).
- Non-sustained ventricular tachycardia: lasting <30 seconds.

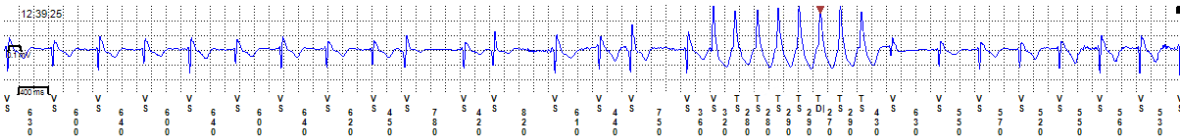

Figure 6. Non-sustained ventricular tachycardia recorded by an implantable loop recorder in a patient with arrhythmic mitral valve prolapse.

8.5.3 Syncope

Syncope is the medical term for fainting or passing out. It is caused by a temporary drop in blood flow to the brain due to a sudden drop in blood pressure, a drop in heart rate, or changes in the amount of blood in areas of the body. Ventricular tachycardias can cause syncope when the heart rate becomes so fast that it impairs the pump function of the heart. A syncope is defined as the following:

- Transient loss of consciousness characterized by a rapid onset, short duration and spontaneous complete recovery.

8.5.4 Ventricular fibrillation or ventricular tachycardia during flecainide treatment

In case of ventricular fibrillation, polymorphic ventricular tachycardia or sustained ventricular tachycardia, flecainide concentration must be assessed concerning overdosing. The clinical personnel should contact a principal investigator and the clinical event will be discussed with expert electrophysiologists on a case-by-case basis. If considered safe, dose adjustment should be preferred over intervention discontinuation.

8.6.5 Ventricular tachycardias detected by implantable loop recorder

We expect to detect several ventricular tachycardias during the course of FLECAPRO. Due to the nature of continuous monitoring, we will likely identify asymptomatic ventricular tachycardias that otherwise would not have been detected, especially since most of the participants would not have a clinical indication for continuous monitoring outside of trial participation. Thus, continuous monitoring in trial participants may significantly influence care and management decisions. Detecting fast ventricular tachycardias on monitoring devices always warrants discussions on initiating or

modifying antiarrhythmic drug treatment or, if severe, considering ICD placement. In the lack of efficacious antiarrhythmic drugs in AMVP, patients with AMVP might be eligible for primary prophylactic ICD. However, the indication for primary prophylactic ICD in the context of AMVP is a matter of debate due to the lack of clinical trials. Consequently, participation in FLECAPRO may increase the likelihood of receiving a primary prophylactic ICD. To mitigate this risk, participants must meet specific criteria to be considered for ICD placement. The considerations and final decision on ICD placement will be discussed in a team including participants from the Steering Committee, a device specialist and electrophysiologist.

ICD placement is warranted in case of:

- ventricular fibrillation
- VT (sustained or non-sustained) with hemodynamic instability

ICD placement should be considered in case of:

- sustained VT at any heart rate
- polymorphic non-sustained VT at any heart rate if lasting more than 5 seconds
- symptomatic non-sustained VT at any heart rate
- asymptomatic non-sustained VT >180 bpm if lasting more than 5 seconds

ICD placement is not warranted in case of:

- asymptomatic non-sustained VTs outside of the above criteria. However, individual characteristics might impact this evaluation and the investigators are inclined to take individual participant characteristics into account.

8.6 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The investigator and any qualified designees are responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE. Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious. When judging whether an AE or SAE is unexpected or not, the Summary of Product Characteristic (SmPC) for flecainide and metoprolol will be used as reference safety information.

The methods for the collection of safety data are described below.

8.6.1 Definitions

8.6.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore by any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. The term AE is used to include both serious and non-serious AEs.

If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant eCRF.

8.6.1.2 Adverse Event of Special Interest (AESI)

In general, AESIs are AEs that occur in categories of special interest with regard to determining the benefit/risk profile and overall safety of a drug.

Sustained ventricular tachycardia, polymorphic ventricular tachycardia or ventricular fibrillation is of special interest, since flecainide has a potential to cause reentry ventricular tachycardias, particularly in patients with myocardial fibrosis. Thus, these events could occur more frequently in the intervention arm. However, these events are typically associated with the disease under study, and they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events are all included in the composite primary endpoint. However, if one of the following conditions applies, then the event must be recorded and reported as an AE/SAE: either the event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the participant; or the investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.6.1.3 Serious Adverse Event (SAE)

An SAE is an AE that fulfils at least one of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the subject or may require medical/surgical intervention to prevent one of the other outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above. These events, or in doubtful cases, should usually be considered serious and reported as SAEs using the important medical event criterion. Hospitalization for administrative reason (for observation or social reasons) is allowed at the discretion of the investigator and will not qualify as serious unless there is an associated adverse event warranting hospitalization.

8.6.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Adverse Reaction: All untoward and unintended responses to an investigational product related to any dose administered.

Unexpected Adverse Reaction: An adverse reaction, the nature of severity of which is not consistent with the applicable product information. This includes an increase in severity, specificity or frequency.

Suspected Unexpected Serious Adverse Reaction: SAE that is unexpected and possibly related to the investigational products. When judging whether a possibly study drug related serious adverse event is unexpected or not, the flecainide or metoprolol SmPC will be used as reference safety information.

8.6.1.5 Medical Device Deficiency (MDD)

Implantable devices (ILRs) are being provided for use in this study. The investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices, and will be reported according to standard procedures at Oslo University Hospital Rikshospitalet.

A Medical Device Deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors and information supplied by the manufacturer. Deficiencies fulfilling the definition of an AE/SAE will follow the process outlined in section 8.4, and deficiencies not fulfilling the definition will be recorded as protocol deviations.

8.6.2 Methods of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.6.3 Recording of AE

If the patient has experienced adverse event(s), the investigator will record the following information in the eCRF:

- The nature of the event(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended date.

The investigator will assess intensity for each event reported during the trial and assign it to one of the following categories according to Common Terminology Criteria for Adverse Events version 4.0:

- **Mild**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate**: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life.
- **Severe**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily life
- **Life-threatening consequences:** Urgent intervention indicated.
- **Fatal**

The causal relationship of the event to the study medication will be assessed as one of the following:

- **Unlikely**: The event is most likely related to etiology other than the investigational product.
- **Possible**: A causal relationship is conceivable and cannot be dismissed.

The outcome of the adverse event (resolved or still ongoing) will be registered. It is important to distinguish between seriousness and severity of AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria for SAE. An AE of severe intensity need not necessarily be considered serious.

8.6.4 Reporting Procedure

8.6.4.1 AE and SAE

All AE and SAE that should be reported will be recorded in the patient's eCRF. SAEs must be reported by the investigator to the Sponsor, Oslo University Hospital, within 24 hours after the site has gained knowledge of the SAE. The Serious Adverse Event Report Form must be completed, documented in the eCRF, signed and sent to the Medical Monitor. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects

by unique trial code numbers assigned to the latter. The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to seriousness, causality and expectedness.

8.6.4.2 SUSAR

Suspected unexpected serious adverse reactions (SUSAR) will be reported to the Norwegian Medicines Agency. The following timelines should be followed:

The sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the Norwegian Medicines Agency in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days. The sponsor shall ensure that other suspected adverse reactions that are serious and unexpected are reported to the Norwegian Medicines Agency and the Regional Committee for Medical Ethics within 15 days of the sponsor after knowledge of the event. The sponsor shall inform all investigators and involved clinicians of suspected adverse reactions that are serious and unexpected. An account of any interruption in treatment, the investigator's assessment of the causal relationship, and consequences for further testing shall accompany the notification of suspected adverse reactions pursuant to the first and second paragraphs.

8.6.5 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESI will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

8.6.6 Pregnancy and Contraceptives

8.6.6.1 Definitions

For the purpose of this protocol, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A pregnant woman is defined as WOCBP that have tested positive on a serum pregnancy test.

8.6.6.2 Mandatory contraceptive use

Both flecainide and metoprolol are not recommended to be used during pregnancy. WOCBP will be informed at screening that we recommend to use contraception (preferably long-acting reversible contraceptives), and that participants should refrain from becoming pregnant, during the trial and until 3 days after discontinuation of study medications. The following contraceptives are accepted (according to Clinical Trials Facilitation and Coordination Group CTFG 21/09/2020 Version 1.1 Recommendations related to contraception and pregnancy testing in clinical trials):

Contraceptive methods considered as highly effective

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral injectable or implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Acceptable contraceptive methods not considered as highly effective

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female and male condom should not be used together.

Participants will be provided with human chorionic gonadotropin (hCG) urine tests free of charge at inclusion and/or at study visits, and urged to confirm absence of pregnancy in case of delayed menstrual period (over one month between menstruations). This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles. Any female participant who becomes pregnant while participating in the study will discontinue study intervention. In case of study drug discontinuation, the patient will still be enrolled in the study.

8.6.6.3 Pregnancy reporting

Pregnancies will be reported by the principal investigator to the sponsor as outlined in section 8.6.4.1. The outcome of the pregnancy will be reported, and information will be collected until three months after delivery, if possible. If a pregnancy has an adverse outcome (i.e. for the mother and/or the baby), an SAE report will be completed. Information about the baby can only be collected upon consent from the parents.

8.7 Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of flecainide as specified in the SoA (section 1.2). A maximum of 2 samples may be collected at additional time points during the course of FLECAPRO if warranted and agreed upon between the investigator and the sponsor. The actual date and time of each sample will be recorded. Participant confidentiality will be maintained.

8.8 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9 Genetics

Genetic analyses are not planned in this study.

8.10 Biomarkers

Blood samples will be collected for baseline characteristics and adequate safety during the course of FLECAPRO. Biomarkers will include Hb, white blood cell count, platelet count, K, Na, glucose, HbA1c, creatinine, eGFR, ALT, AST, bilirubin, albumin, INR, NT-proBNP and troponin T. Samples will be collected according to the schedule described in the SoA.

Extra blood samples will be taken, appropriately labeled and stored in a study specific biobank at Oslo University Hospital. FLECAPRO study personnel will have access to the samples, as well as the respective analysis units. Samples will be marked with trial specific code, and only FLECAPRO study personnel have access to the code list. Sponsor will within 2 years after end of trial (defined as last patient last visit, expected to occur December 31 2025) submit and receive approval for further use of the samples (general biobank with a separate consent form), and if not, the samples in the study specific biobank will be destroyed within 2 years after end of trial.

8.11 Immunogenicity Assessments

Not applicable.

8.12 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9.0 Statistical Considerations

A separate detailed Statistics Analysis Plan (SAP) will be developed in collaboration with the dedicated study statistician employed by the Clinical Trial Unit at Oslo University Hospital before data lock.

The first main statistical analysis is planned when the last patient has completed the end-of-study visit 26 months after randomization. The number and severity of adverse events will be assessed consecutively. Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until the day of database lock.

9.1 Statistical Hypothesis

The primary objective is to demonstrate that flecainide and metoprolol is superior to metoprolol alone in achieving a reduced number of ventricular tachyarrhythmias at 12 months.

The null hypothesis of no difference in number of ventricular tachyarrhythmias between flecainide and metoprolol, and metoprolol alone, will be tested:

- H0: There is no difference in number of ventricular tachyarrhythmias between flecainide and metoprolol, and metoprolol alone.
- H1: There is a non-zero difference in number of ventricular tachyarrhythmias between flecainide and metoprolol, and metoprolol alone.

The null hypothesis will be tested for superiority, with two-sided tests and confidence level equal to 0.05.

9.2 Population for Analysis

The following populations will be considered for the analyses:

- **Intention-to-treat (ITT) population:** All randomized participants, regardless of protocol adherence.
    - This population will be used to assess superiority for the primary endpoint and key secondary endpoints.
- **Safety population:** All patients who have been enrolled in the trial, and who have received at least one dose of flecainide.

- This population will be used to assess the secondary safety endpoints

- **Per-protocol population:** All participants who have completed 26 months of treatment and taken study drug according to the protocol.
  - This population will be used for sensitivity analyses of the primary endpoint.

9.3 Statistical Analysis

The Statistical Analysis Plan will be finalized prior to completion of the study and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Dedicated study statistician will be employed via the Clinical Trial Unit at Oslo University Hospital for the entire study period.

9.3.1 Primary Endpoint

We will test superiority for the primary endpoint in the intention-to-treat population using a generalized linear mixed model with Poisson regression at the 0.05 significance level. Random effects for the patient ID will be used to account for repeated measurements given by the crossover design. Based on the preliminary data, we expect some patients to have zero primary endpoints in the intervention arm, which could lead to challenges when using Poisson regression. Thus, zero-inflated models or negative binomial regression would be needed, or a binary outcome in case most patients have no endpoints during the intervention arm (for details see SAP).

9.3.2 Pre-defined subgroup analyses

Certain characteristics are associated with higher incidence of ventricular arrhythmia. We trust the randomization and crossover study design for balanced allocation in sequencing of study arms. However, interaction effects in subgroups of interest will be assessed in the study:

- Females or males
- Normal or reduced left ventricular ejection fraction at baseline
  - Cut off 55%
- Normal or abnormal left ventricular end-diastolic diameter
  - Cutoff 58 mm for males and 52 mm for females
- No/trivial or moderate/severe mitral regurgitation
- Presence or absence of mitral regurgitation
- Unileaflet or bileaflet mitral valve prolapse

- Presence or absence of mitral annular disjunction
- Presence or absence of late gadolinium enhancement
- Monofocal or multifocal premature ventricular complexes
- Presence or absence of connective tissue disease
- BMI ≥30 or BMI <30.
- ICD vs no ICD at inclusion
- Presence or absence of prior aborted cardiac arrest
- Presence or absence of T-wave inversions on ECG

9.3.3 Key Secondary Endpoints

The rates of the predefined key secondary endpoints will be tested in a hierarchical order, meaning that hypothesis testing stops at the first non-significant endpoint ($p \geq 0.05$).

Generalized linear models will be used for the secondary endpoints, specifically linear models for continuous variables, logistic models for binary variables, Poisson for count variables. Random effects for the patient ID will be used to account for repeated measurements.

9.3.4 Secondary Safety Endpoints

Safety analyses will include tabulation of type and frequency of all adverse events. Any serious adverse events will be reported with comprehensive narratives. Any value of safety laboratory parameters outside normal ranges will be identified.

9.3.5 Exploratory Secondary Endpoints

The secondary endpoints defined as “exploratory” in the protocol will be tested and interpreted as hypothesis generating.

9.3.6 Missing Data

Every reasonable effort will be made to minimize missing data. Some data may be missing completely at random (MCAR) and missing at random (MAR). However, some instances of data missing not at random (MNAR) may occur:

- *Availability for analysis*
  - If either the intervention (flecainide and metoprolol) increases likelihood of being available for analysis by decreasing incidence of ventricular tachycardia, or decreases the likelihood of being available for analysis by increasing incidence of Safety Composite.
- *Allocation to treatment sequence*
  - If study intervention increases quality-of-life as hypothesized, increased dropout may occur in participants sequenced to be treated with intervention first and control second.

This is especially true if participants experienced AEs on metoprolol or other beta blockers prior to enrollment.

- Similarly, increased dropout may occur in participants sequenced to be treated with control first and intervention second, as participants have to wait for 13 months to start potential effective treatment.

- *Missing cardiac magnetic imaging data*
  - Participants in FLECAPRO are likely to have a high burden of premature ventricular complexes that might interfere with CMR image acquisition causing missing CMR data. Additionally, some participants might have unconditional cardiac devices prior to inclusion and thus a contraindication to CMR.

Because of this, we will take conservative and simplistic measures to handle missing data. The mixed model framework generally accounts for missing data that are MAR, but given the above, we will also perform sensitivity analysis imputing the missing data with methods that do not rely on the assumption of "missing-at-random", such as "last-observation-carried-forward" and "worst-case" imputation.

In particular, missing data on the primary endpoint analyses will be replaced using multiple imputation models (for details see Statistical Analysis Plan). In case of missing data on Holter monitoring or questionnaires (whole questionnaire or single questions), a baseline observation carried forward single imputation will be used.

Sensitivity analysis for the primary endpoints will be performed on the complete-case data and on the worst-case imputation data. Additional post-hoc sensitivity analyses will be performed if unexpected patterns of missing data are observed.

9.4 Interim Analysis

Interim analysis has not been planned.

9.5 Sample Size Determination

Sample size estimates are calculated based on limited previous data from the same population. For an individual patient, the primary endpoint can be expected to occur at least 3 times during the control arm based on a previous case series[21]. On the contrary, there is limited data on the occurrence of the primary endpoint in the intervention arm. Because of the potential proarrhythmic effect of flecainide, side effects and relatively soft primary endpoint, we consider a 60% reduction in the primary endpoint clinically relevant. A 60% reduction is a realistic effect size based on our previous data on flecainide use in the same population[21].

There is no standard method to calculate sample size for a count based endpoint in a crossover setting. However, to obtain 80% power with a two-sided 0.05 alpha for a 60% reduction in the primary endpoint in the intervention group, these two sample size calculations have been used:

- 14 patients should complete the study when using simulation without excess zeros.
- 22 patients should complete the study when using simulations with excess zeros.

Both methods have their limitations. Firstly, the simulations are based on data from a limited case series[21]. There is larger heterogeneity in the patient population included in FLECAPRO, and, consequently, a possibility that subgroups of patients do not show the same efficacy seen in the case series. Thus, using strict sample size estimates from these simulations could lead to a clinically underpowered study. Secondly, if the hypothesis of FLECAPRO holds true, we expect the primary endpoint not to occur in some patients during the intervention arm. Because of this, statistical methods that do not account for excess zeros could prove inadequate. For further details see SAP.

Because of these limitations, we plan for a conservative approach to sample size calculation and will plan for 40 patients to complete the study. Based on the simulations, this number will not lead to a mathematically underpowered study, while also taking into account a larger heterogeneity in the patient population. We expect 25% dropout, and thus, we will enroll a maximum of 50 participants such that approximately 40 evaluable participants complete the study.

A 25% dropout rate is high, but we believe this to be relevant. Firstly, if the hypothesis of FLECAPRO holds true, the crossover study design may cause patient randomized to intervention arm first to drop out during the control arm if developing side effects. Secondly, severe ventricular tachyarrhythmias may occur in both study arms during the course of FLECAPRO, potentially leading to treatment discontinuation.

10.0 Supporting Documentation and Operational Considerations

10.1 Regulatory and Ethical and Study Oversight Considerations

This study will be conducted in accordance with the protocol and with the following:

- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable national laws and regulations

Registration of patient data will be carried out in accordance with national personal data laws.

10.1.1 Ethical Considerations for Participants

If the hypothesis of the study is correct, participants will receive superior treatment during half of the study period. This constitutes a significant benefit.

Individuals who consent to the study will commit to additional visits at the academic institution, with travel cost and risk. They will also contribute with personal information, and thereby trust the sponsor to treat their data appropriately.

The active protocol will include a study-specific invasive procedure with implantation of a loop recorder and possibly invasive coronary angiography (the latter only if participants have symptoms and risk factors for coronary artery disease at screening). The CT coronary angiography and cardiac magnetic resonance imaging will expose the participants to a contrast agent and a radiation dose (radiation only for the former) over the regular clinical course. However, the contrast dose is low and overt renal damage is very uncommon after contrast-enhanced CT or cardiac MRI.

10.1.2 Ethics Committee Approval

The regional ethics committee must approve the study protocol, including the patient information and informed consent form to be used, before enrollment begins. The investigator is responsible for informing the regional ethics committee of any major amendments to the protocol as per national requirements.

10.1.3 Financial Disclosure

FLECAPRO is an investigator-sponsored study. The trial is funded by the South-Eastern Norway Regional Health Authority through a grant (#2024024), and by ProCardio Center for Innovation, Oslo University Hospital, through the Research Council of Norway. We will not apply for funding from industry outside of providing implantable loop recorders (Medtronic). The authors have no commercial interest or economic disclosure related to the project. The investigators take sole responsibility for the integrity of the data, the writing of the manuscript and the dissemination of the results. Medtronic will have neither influence on the data collection or analyses, nor writing of the manuscript.

10.1.4 Informed Consent Procedure

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. Participants will be informed that their participation is voluntary and that the participant is allowed to refuse further participation in the protocol whenever he/she wants for any reason. This will not prejudice the patient’s subsequent care. Participants will be required to sign a statement of informed consent before enrollment in the study. This will be done in accordance with the national and local regulatory requirements. A copy of the informed

consent will be provided to the participant. The signed and dated consent forms will be filed in the Investigator Site File binder.

Participants who are rescreened are required to sign a new informed if rescreening occurs after 3 months of the previous informed consent signature date.

10.1.5 Recruitment Procedure

The population available for screening in FLECAPRO will be:

- All consecutive patients with symptomatic arrhythmic mitral valve prolapse at scheduled follow-up at the Outpatient Clinic at Department of Cardiology, Oslo University Hospital, Rikshospitalet.
- All patients with mitral valve prolapse admitted to the Department of Cardiology at Oslo University Hospital, Rikshospitalet, due to symptomatic ventricular arrhythmias.

Cardiologists at surrounding hospitals will be informed about the trial and the possibility to refer patients to our outpatient clinic for evaluation and possible participation.

A principal investigator or study nurse will approach the participant to give additional information and obtain informed consent. A principal investigator could have a prior clinical relationship with the potential participant. Potential participants will get written and oral information about the trial at a physical visit at Department of Cardiology, Oslo University Hospital, Rikshospitalet. They will be given as much time as needed to decide whether to participate in FLECAPRO.

10.1.6 Data Protection

All clinical trial information will be recorded, processed, handled, and stored by the Sponsor in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the participants remain protected in accordance with the given permissions by the Ethics Committee and Personal Data Officer at Oslo University Hospital and applicable law on personal data protection (Regulation (EU) 2016/679, General Data Protection Regulation, GDPR). Appropriate technical and organizational measures will be implemented to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves the transmission over a network. The data will not be used for economic benefit nor be made available for commercial actors. Patients will be informed that his/her medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

10.1.6.1 Electronic Case Report Forms (eCRF)

FLECAPRO will use an online electronic Case Report Form (eCRF) on the Viedoc® platform. The designated investigator staff will enter the data required by the protocol into the eCRF. The Principal

Investigator is responsible for assuring that data entered into the eCRF are complete, accurate, and that entry is performed in a timely manner. If any assessments are omitted, the reason for such omissions will be noted in the eCRFs. Corrections, along with the reason for the corrections, will also be recorded. After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

10.1.6.2 Source Data

Some data will be recorded directly into the eCRF, which together with the patient electronic medical record, is to be considered the source data. All data important for patient safety and continued care must be duplicated in the patient's medical record as described below. Study-specific imaging data, ILR data and blood analyses are independent source data.

The medical records of each patient should clearly describe at least:

- That the patient is participating in the study
- Date when the informed consent was obtained from the patient
- Results of all assessments confirming a patient's eligibility for the study
- Disease (past and current; both the disease studied and others, as relevant)
- Relevant allergy or intolerance
- Surgical history, as relevant
- Treatments withdrawn/withheld due to participation in the study
- Results of assessments performed during the study
- Treatment provided, changes in treatments during the study and the time points for the changes
- Visits to the clinic/telephone contacts during the study, including those for study purposes only
- Adverse Events and Serious Adverse Events (if any) including causality assessments
- Date of, and reason for, discontinuation from the study treatment
- Date of, and reason for, withdrawal from the study
- Date of death and cause of death if available

10.1.6.3 Database Management

Data will be entered into the eCRF without delay and stored in the dedicated and secure online platform (Viedoc®). Data will be extracted from Viedoc® for analysis, and the extracted data will be stored in dedicated, secure areas. Data will be stored in a pseudonymised manner, where each study participant is recognizable by his/her unique trial subject number. The data will be stored until 31st of November 2050 in compliance with local regulations, or until the patient requires that his/her data are deleted. Data in the eCRF will be handled according to GCP. Only the personnel authorized to enter and/or analyze data (i.e. investigators) will have access to the database.

10.1.6.4 Data Sharing

In agreement with good research ethics, we will share anonymized data sets with the medical community via the medical journal upon submitting the manuscript.

10.1.8 Study Monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check that the study is conducted as approved by the Ethics Committee and adhere to Good Clinical Practice (GCP) guidelines.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

Study monitoring will be performed by the Clinical Trial Unit, Oslo University Hospital.

10.1.9 Data Monitoring Committee and Safety Data Review

Participant safety will be continuously monitored by the Data Monitoring Committee, which includes safety signal detection at any time during the study. The Data Monitoring Committee is independent from the Sponsor and will be composed of individuals with no competing interest and regard to the study investigational products or study outcome. The committee consists of two independent clinicians and a statistician. It will receive written reports summarizing patient recruitment, the number of AEs/SAEs and the registered occurrence of the primary endpoint and secondary safety endpoint (safety composite) after the first 5 patients have been randomized, and once every 6 months thereafter. They will be encouraged to assess signals of safety without hypothesis testing. The committee will have access to the randomization code, and can perform an interim analysis regarding the number of adverse events and serious adverse events if they find it necessary. The Data Monitoring Committee will receive additional information on demand and can advise temporary or permanent stop in patient enrollment. In case there is worry of a pattern of worse ventricular arrhythmia outcome, a recommendation to abort the study will be given to the Sponsor.

If moderate or severe AEs are consistently observed across participants by the medical monitor, the dose escalation will be temporarily halted and no further participants will be dosed until a full safety review of the study has taken place. The same is true if unacceptable pharmacological effects reasonably attributable to flecainide or metoprolol in the opinion of the investigator are observed in several of the participants. The number of such effects will be at the discretion of the Data Monitoring Committee. Relevant reporting and discussion with the Medical Monitor and Data Monitoring Committee will take place before resumption of dosing.

If severe ventricular tachyarrhythmias occur during treatment with flecainide, the Investigator will consult the Data Monitoring Committee before deciding to discontinue flecainide.

10.1.10 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period permitted by each hospital. The study documentation (eCRFs, etc.) shall be retained and stored during the study and for 25 years after last patient visit. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel, in accordance to local regulations.

10.1.11 Trial Registration

The Clinical Trial Information System (CTIS) will be the primary registry of the trial.

10.1.12 Trial insurance

The Principal Investigator has insurance coverage for this study through the Norwegian Pasientskadeloven. Insurance for the intervention will be obtained from Legemiddelforsikringen.

10.1.13 Cost-benefit Consideration

The project will need considerable funding for thorough and precise execution. Any unforeseen events may also impose a cost to the public hospital system. The cost of medication is not negligible. On the other side, the potential economic benefits from reducing ventricular arrhythmic burden, frequent hospital visits and patient symptoms are substantial. Therefore, our general consideration is that this project holds great potential for improved cost-benefit in the long-term.

10.1.14 Publication Policy

The results of this study will be submitted for publication and posted in a publicly assessable database of clinical study results. We will allow for a separate publication of study design, rationale and baseline characteristics once all subjects have been enrolled.

The results of this study will also be submitted to the Competent Authorities and the Regional Ethics Committees according to EU and national regulations. All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors. The principal investigator will be first or last author. The funding sources have had no role in the conception of the study. Neither will the funding sources participate in the implementation of the study, in the analyses of the results, or in the decision to publish.

All manuscript authors of the main analysis and spin-off projects must be according to ICMJE recommendations and must be approved by the Steering Committee.

10.1.15 Cost

Participants will receive a refunded prescription of metoprolol and flecainide based on the current approved treatment indication.

All patients enrolled in the study will receive implantable loop recorder. A loop recorder (LINQ II) will cost approximately 15.000 NOK for the study duration for one patient. The total cost of loop recorders in FLECAPRO will be approximately 750.000 NOK. The Sponsor will provide the loop recorders, in collaboration with Medtronic (Minneapolis, USA) via a research consortium (ProCardio Center for Innovation).

All patients enrolled in the study will undergo cardiac magnetic resonance (CMR) at baseline if not contraindicated (e.g. due to non-compatible ICD) or done within the last 2 years prior to inclusion. We will perform CMR in all patients randomized to receive the intervention arm as the last treatment period. Additionally, we will perform CMR in 10 patients without prior ICD shortly after ILR implantation. A CMR will cost approximately 3.000 NOK for one examination of one patient. The total cost of CMR in FLECAPRO will be approximately 255 000 NOK.

10.2 Spin-offs

Spin-off projects are analyses planned around the primary inclusion database. Projects that are not pre-defined must be approved by the Steering Committee and Partners after written project proposal. Spin-off projects will have a dedicated supplementary protocol.

Planned spin-off analyses:

- Assessment of left ventricular reverse remodeling following flecainide therapy.
  - In addition to performing echocardiography after each treatment period, we will perform an additional CMR in patients randomized to the intervention arm as the last treatment period (after ILR has been removed). The CMR will be performed to assess whether markers of diffuse fibrosis decreases after suppression of ventricular arrhythmias.
- The implication of ILR on measurement of T1-times.
  - We will ask 10 participants to undergo an additional CMR exam shortly after implantation of ILR to assess whether ILR affects the magnetic field in a way that markers of diffuse fibrosis cannot be measured reliably.
- Association between change in health-related quality of life (SF-36 and HADS) and arrhythmic burden by Holter or LINQII.
- Association between PVC count on Holter monitoring and LINQ II.

- Participants will be assessed by Holter monitoring 6 times during the course of FLECAPRO (300 in total 50 participants). We will assess the validity of the PVC algorithm of LINQ II compared to Holter monitoring.

10.3 Partners

Partners are collaborating units with their associated contact person. They have key roles in the main study and can propose subsequent spin-off studies.

10.3.1 Section for Outpatient Clinic, Oslo University Hospital, Rikshospitalet

The section for outpatient clinic at Department of Cardiology is a large outpatient clinic treating and following patients with genetic cardiac disease, survivors of cardiac arrest and other arrhythmic disorders. The section treats 2500 outpatients every year, and is the only center in Norway having clinical experience with arrhythmic mitral valve prolapse. Qualified and dedicated cardiologists contribute to screening, inclusion and follow-up.

- Kristina H Haugaa, MD PhD, Head of Section

10.3.2 ProCardio Center for Innovation, Oslo University Hospital, Rikshospitalet

ProCardio Center for Innovation is a newly established Center for Research-based Innovation funded through the Research Council of Norway. At ProCardio, researchers and industrial partners work together to ensure that ideas become products that benefit patients, which is led by internationally renowned researchers including fields of cardiogenetics, sudden cardiac death and arrhythmic mitral valve prolapse. The ILRs provided by Medtronic is through this research consortium.

- Kristina H Haugaa, MD PhD, Center Director

10.3.3 Section for Electrophysiology, Oslo University Hospital, Rikshospitalet

The section for electrophysiology at the Department of Cardiology is the largest electrophysiological laboratory in Norway. More than 1600 electrophysiological exams and ablations are performed every year, as well as 350 cardiac device implantations every year. The section has experience in management and follow-up of patients with arrhythmic mitral valve prolapse. Qualified and dedicated electrophysiologists contribute with study planning, endpoint assessment and implantation of cardiac devices.

- Erik Kongsgård, MD PhD, Head of Section

10.3.4 Section for Echocardiography, Oslo University Hospital, Rikshospitalet

The section for echocardiography at the Department of Cardiology is the largest echocardiographic laboratory in Norway and has international accreditation. More than 10.000 echocardiographic

exams are performed every year, including on many patients with mitral valve prolapse. Qualified and dedicated echocardiographers and technicians contribute with acquisitions and interpretations of optimal quality.

- Helge Skulstad, MD PhD, Head of Section

10.3.5 Department of Radiology and Nuclear Medicine, Oslo University Hospital, Rikshospitalet

The Department of Radiology and Nuclear Medicine at Oslo University Hospital has state-of-the-art modern CT and MRI scanners. They have good accessibility for high-end CMR and will perform and evaluate all CT and CMR data. The Department will also conduct planned spin-offs.

- Einar Hopp, MD PhD, Head of Department

10.4 Study Committee Structure and Contact Details

- Principal Investigator:
  - Dr. Eivind W Aabel, Oslo University Hospital
    - +4741243148 // e.w.aabel@medisin.uio.no
- Steering Committee:
  - Prof. Kristina H Haugaa, Oslo University Hospital
    - kristina.haugaa@medisin.uio.no
  - Dr. Erik Kongsgård, Oslo University Hospital
    - ekongsga@ous-hf.no
  - Dr. Erik Lyseggen, Oslo University Hospital
    - elysegge@ous-hf.no
  - Dr. Øyvind H Lie, Oslo University Hospital
    - oyvlie@gmail.com
  - Dr. Nina E Hasselberg, Oslo University Hospital
    - nihass@ous-hf.no
- Medical Monitor:
  - Dr. Erik Lyseggen, Oslo University Hospital
    - +4748603200 // elysegge@ous-hf.no
- Endpoint Adjudication Committee:
  - Dr. Ane Cecilie Dale, cardiologist, St. Olavs Hospital, Trondheim, Norway
    - ane.cecilie.dale@stolav.no
  - Dr. Brage H Amundsen, cardiologist, St. Olavs Hospital, Trondheim, Norway
    - brage.hoyem.amundsen@stolav.no
  - Dr. Stian Ross, cardiologist, Oslo University Hospital, Oslo, Norway

        - stross@ous-hf.no

- Study Statistician:
    - Nina Gunnes, statistician, Oslo University Hospital, Oslo, Norway
        - ninagu@ous-hf.no
- Data Monitoring Committee:
    - Prof. Torbjørn Omland, cardiologist, Akershus University Hospital, Nordbyhagen, Norway
        - torbjorn.omland@medisin.uio.no
    - Prof. Jan Pål Loennechen, cardiologist, St. Olavs Hospital, Trondheim, Norway
        - jan.pal.loennechen@stolav.no
    - Inge Christoffer Olsen, external statistician, Oslo University Hospital, Oslo, Norway
        - inge.christoffer.olsen@gmail.com

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12.0 Signature Page

I hereby declare that I will conduct the study in compliance with this protocol and the applicable regulations:

Name	Title	Role	Date	Signature
Eivind W Aabel	MD, PhD	Principal Investigator		
Erik Lyseggen	MD, PhD	Medical Monitor		
Christian Five	MD	Sub-investigator		
Cecilie Bugge	MD	Sub-investigator		
Thea Dalen	RN	Study Nurse		
Emilie	RN	Study Nurse		