Załącznik nr 1 do uchwały Nr 24 Senatu UMK z dnia 25 lutego 2025 r.

WNIOSEK PROJEKTU DOKTORSKIEGO

Szkoła Doktorska Nauk Medycznych i Nauk o Zdrowiu

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CZĘŚĆ A: OPIS PROJEKTU

1. TEMAT PROJEKTU
Effects of Baxdrostat on Cardiac Fibrosis, Inflammation, and Ventricular Remodeling Following Myocardial Infarction
2. STRESZCZENIE PROJEKTU (max. 1000 znaków)
This multicenter, randomized, active-comparator, cross-over study will evaluate the effects of baxdrostat, a highly selective aldosterone synthase inhibitor, versus spironolactone on biological pathways involved in post-myocardial infarction cardiac remodeling. Patients will be randomized to receive either baxdrostat or spironolactone for 1 month, followed by cross-over to the alternative treatment for an additional month. The primary objective is to compare the effects of both therapies on a focused panel of biomarkers reflecting myocardial fibrosis, remodeling, inflammation, and ongoing cardiac injury, including soluble ST2 (sST2), galectin-3, procollagen type III N-terminal propeptide (PIIINP), collagen type I telopeptide (CITP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin (hs-cTn), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP). Secondary endpoints will include endothelial function, body composition, and ambulatory blood pressure. By targeting aldosterone biosynthesis upstream of mineralocorticoid receptor blockade, baxdrostat may provide more comprehensive suppression of profibrotic, proinflammatory, and vascular injury pathways involved in adverse post-infarction remodeling compared with conventional mineralocorticoid receptor antagonism.
3. CEL NAUKOWY PROJEKTU I ZNACZENIE PODJĘTEGO PROBLEMU BADAWCZEGO (max. 3000 znaków)
Adverse cardiac remodeling following myocardial infarction (MI) remains a major cause of heart failure, recurrent hospitalization, and premature mortality. Persistent activation of the renin–angiotensin–aldosterone system, particularly aldosterone excess, promotes myocardial fibrosis, inflammation, endothelial dysfunction, and progressive deterioration of cardiac function. Although mineralocorticoid receptor antagonists (MRAs), such as spironolactone, improve outcomes in selected patients, they do not suppress aldosterone production and their use may be limited by hyperkalemia, renal dysfunction, and endocrine adverse effects. Baxdrostat is a novel, highly selective aldosterone synthase inhibitor that suppresses aldosterone biosynthesis by targeting CYP11B2. By acting upstream of the mineralocorticoid receptor, baxdrostat may provide more comprehensive inhibition of

aldosterone-mediated tissue injury than conventional MRAs. However, its potential role in post-infarction remodeling has not been investigated.
The primary objective of this project is to compare the effects of baxdrostat and spironolactone on biological pathways involved in post-MI cardiac remodeling. In a multicenter, randomized, active-comparator, cross-over study, patients will receive both treatments sequentially, enabling direct within-patient comparison. The study will assess biomarkers reflecting myocardial fibrosis, remodeling, inflammation, and cardiac injury, including sST2, galectin-3, PIIINP, CITP, NT-proBNP, high-sensitivity cardiac troponin, interleukin-6, and high-sensitivity C-reactive protein. Secondary endpoints will include endothelial function, body composition, and ambulatory blood pressure.
The project addresses an important gap in cardiovascular medicine. It remains unknown whether inhibition of aldosterone synthesis offers advantages over receptor blockade in reducing mechanisms responsible for adverse remodeling after MI. The results may improve understanding of aldosterone-mediated cardiovascular injury and provide the first mechanistic clinical evidence supporting future studies of baxdrostat in patients at risk of developing heart failure. Given the growing burden of heart failure despite contemporary therapy, identification of more effective strategies to limit post-infarction remodeling is of substantial scientific and clinical importance.

4. KONCEPCJA I PLAN BADAŃ Z UWZGLĘDNIENIEM METODYKI (max. 4000 znaków)

The project is designed as a prospective, multicenter, randomized, open-label, active-comparator, cross-over clinical study evaluating the effects of baxdrostat and spironolactone on post-myocardial infarction cardiac remodeling.
The study will be conducted in three participating centers: University Hospital No. 1 Dr. Antoni Jurasz in Bydgoszcz, Stanisław Staszic Specialist Hospital in Piła, and Polish Baptism Memorial Hospital in Gniezno.
Adult patients hospitalized due to their first lifetime myocardial infarction and treated according to current guidelines will be eligible for inclusion. Following stabilization, participants will be randomized in a 1:1 ratio to receive either baxdrostat or spironolactone for the first month of treatment. After completion of the first treatment period, patients will cross over to the alternative therapy for an additional month. Randomization will be performed centrally using a computer-generated allocation sequence.
The primary objective is to compare the effects of aldosterone synthase inhibition and conventional mineralocorticoid receptor antagonism on pathways involved in adverse cardiac remodeling. The primary endpoint will be NT-proBNP concentration measured after each treatment period.
Secondary mechanistic endpoints will include changes in biomarkers reflecting myocardial fibrosis, extracellular matrix turnover, inflammation, and myocardial injury, including soluble ST2 (sST2), galectin-3, procollagen type III N-terminal propeptide (PIIINP), collagen type I telopeptide (CITP), high-sensitivity cardiac troponin, interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP).
Additional assessments will include endothelial function, ambulatory blood pressure monitoring, body composition analysis, renal function, serum electrolytes, and

comprehensive echocardiography, including left ventricular ejection fraction, ventricular volumes, and global longitudinal strain.
Clinical efficacy endpoints will include development or worsening of heart failure symptoms requiring treatment intensification, hospitalization for heart failure, and all-cause mortality. Safety endpoints will include clinically relevant hypotension, hyperkalemia, hypokalemia, deterioration of renal function, and any adverse event requiring dose modification or treatment discontinuation.
Blood sampling and clinical assessments will be performed at baseline, after the first month of treatment (before cross-over), and at study completion. This design will enable both within-patient and between-treatment comparisons while minimizing interindividual variability.
An interim analysis will be performed after enrollment of the first 30 patients (15 per treatment sequence). This analysis is necessary because no previous clinical studies have evaluated the effects of baxdrostat on post-myocardial infarction remodeling biomarkers or related mechanistic endpoints. Consequently, reliable estimates of effect size and variability required for formal sample size calculation are currently unavailable. The interim analysis will provide preliminary estimates of treatment-related changes in NT-proBNP and other biomarkers, enabling a robust power calculation. Based on these results, the final study population size will be determined to ensure adequate statistical power while avoiding both underpowered and unnecessarily oversized recruitment. As this will be the first randomized mechanistic study of baxdrostat in patients after myocardial infarction, such an adaptive design is scientifically justified and methodologically appropriate.
The proposed study will provide the first direct comparison of aldosterone synthase inhibition and mineralocorticoid receptor antagonism in the early post-infarction period and may identify novel strategies for preventing adverse cardiac remodeling and subsequent heart failure development.

5. SPODZIEWANE ZNACZENIE WYNIKÓW BADAŃ (max. 1500 znaków)

The proposed study is highly innovative because it will be the first randomized clinical investigation evaluating the biological effects of selective aldosterone synthase inhibition with baxdrostat in patients following myocardial infarction. While the role of aldosterone in post-infarction remodeling is well established, no clinical study has directly compared upstream suppression of aldosterone biosynthesis with conventional mineralocorticoid receptor antagonism in this setting.
The project is expected to provide novel mechanistic insights into the effects of baxdrostat on myocardial fibrosis, inflammation, endothelial dysfunction, and adverse cardiac remodeling. By combining biomarker profiling, endothelial function assessment, body composition analysis, echocardiography, and clinical outcome evaluation, the study will offer a comprehensive characterization of aldosterone-mediated pathways during the early post-infarction period.
The results may identify biomarkers particularly sensitive to aldosterone synthase inhibition and improve understanding of mechanisms responsible for progression from myocardial infarction to heart failure. Importantly, the study will generate the first clinical data supporting or refuting the hypothesis that inhibition of aldosterone synthesis provides advantages over conventional receptor blockade.

Beyond its scientific value, the project has significant translational potential. The findings may form the basis for future large-scale randomized trials evaluating baxdrostat as a novel strategy for prevention of adverse cardiac remodeling and heart failure after myocardial infarction. Consequently, the study may contribute to the development of more effective post-infarction therapies and help address the persistent residual risk that remains despite contemporary guideline-directed medical treatment.
6. PLANOWANA FORMA ROZPRAWY DOKTORSKIEJ ☐ MANUSKRYPT X CYKL PUBLIKACJI ☐ TRYB HYBRYDOWY