Although progress has been made in reducing the size of myocardial infarcts (MIs) using urgent revascularization, once a substantial infarct occurs, the risk of ventricular remodeling and subsequent heart failure is significant.1–4 Recent advances in pharmacological treatment, with neurohormonal inhibition, can modestly improve this risk.5,6 However, there remains an unmet medical need to markedly reduce or eliminate the risk of ventricular remodeling and development of heart failure following extensive acute MI.6

Left ventricular (LV) remodeling after MI is characterized by inflammation, fibrosis, and continuous and progressive degradation of the extracellular matrix.7,8 Recent experiments

Background—We aimed to test, for the first time, the feasibility of intracoronary delivery of an innovative, injectable bioabsorbable scaffold (IK-5001), to prevent or reverse adverse left ventricular remodeling and dysfunction in patients after ST-segment–elevation myocardial infarction.

Methods and Results—Patients (n=27) with moderate-to-large ST-segment–elevation myocardial infarctions, after successful revascularization, were enrolled. Two milliliters of IK-5001, a solution of 1% sodium alginate plus 0.3% calcium gluconate, was administered by selective injection through the infarct-related coronary artery within 7 days after myocardial infarction. IK-5001 is assumed to permeate the infarcted tissue, cross-linking into a hydrogel and forming a bioabsorbable cardiac scaffold. Coronary angiography, 3 minutes after injection, confirmed that the injection did not impair coronary flow and myocardial perfusion. Furthermore, IK-5001 deployment was not associated with additional myocardial injury or re-elevation of cardiac biomarkers. Clinical assessments, echocardiographic studies, 12-lead electrocardiograms, 24-hour Holter monitoring, blood tests, and completion of Minnesota Living with Heart Failure Questionnaires were repeated during follow-up visits at 30, 90, and 180 days after treatment. During a 6-month follow-up, these tests confirmed favorable tolerability of the procedure, without device-related adverse events, serious arrhythmias, blood test abnormalities, or death. Serial echocardiographic studies showed preservation of left ventricular indices and left ventricular ejection fraction.

Conclusions—This first-in-man pilot study shows that intracoronary deployment of an IK-5001 scaffold is feasible and well tolerated. Our results have promoted the initiation of a multicenter, randomized controlled trial to confirm the safety and efficacy of this new approach in high-risk patients after ST-segment–elevation myocardial infarction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01226563.

Key Words: coronary disease n heart failure n myocardial infarction n ventricular remodeling
WHAT IS KNOWN

- Left ventricular remodeling after myocardial infarction (MI) is characterized by progressive degradation of the extracellular matrix.
- IK-5001 (BioLineRx, Jerusalem, Israel) is a novel, injectable, bioabsorbable scaffold that when injected into the infarct-related coronary artery, selectively enters the infarcted tissue and then cross-links to form a hydrogel.
- Intracoronary injection of IK-5001 scaffold has been shown to prevent left ventricular remodeling and preserve left ventricular function in large animal models of MI.

WHAT THE STUDY ADDS

- This report describes the results of a pilot study of the first 27 patients treated with IK-5001, a novel self-assembling, self-disassembling temporary bioabsorbable cardiac scaffold.
- Intracoronary deployment of an IK-5001 scaffold within the first week after ST-segment-elevation myocardial infarction is feasible and well tolerated.

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in small and large animals have suggested that direct injection of biomaterials, such as alginate, fibrin, collagen, and self-assembling peptide, into the infarct, could act as a stabilizer to internally constrain the infarcted segment from expanding, thereby limiting LV remodeling.\(^9,14\)

IK-5001 (BioLineRx, Jerusalem, Israel) is an injectable device comprising a solution of 1% sodium alginate plus 0.3% calcium gluconate which, when injected into the infarct-related coronary artery, selectively enters and permeates the infarcted myocardial tissue. Then, it reversibly cross-links into a hydrogel in a calcium-dependent manner in situ, thereby forming a temporary bioabsorbable cardiac scaffold that functions as an artificial extracellular matrix.\(^9,10\) The selectivity of deposition within the infarct zone is ascribed to the abnormal microvascular permeability and elevated extracellular calcium concentrations characteristic of acute MI.\(^15,16\) Intracoronary injection of IK-5001 scaffold (previously referred to as BL-1040) has been shown to prevent LV remodeling and enlarge and preserve LV function in a swine model of MI.\(^9\) IK-5001 scaffold was subsequently resorbed as myocardial extracellular calcium declined and was excreted unchanged via the kidney.\(^9,10,17\)

The aim of the present study was to test the feasibility of intracoronary delivery of IK-5001 in patients recovering from a large MI. The present report describes the first human experience using IK-5001 in survivors of a moderate-to-large MI, and its findings could open up new options in the treatment of LV remodeling and heart failure after MI.

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**Methods**

This study was performed in accordance with accepted principles of clinical research, the Declaration of Helsinki, and the International Conference on Harmonisation. It was performed at selected sites in Belgium and Germany. The listing of participating centers and primary investigators can be found in the Data Supplement. All patients provided informed consent.

**Patient Population**

This study was designed to include patients who had survived first, moderate-to-large MI, and who had undergone successful recanalization with percutaneous coronary intervention (PCI). The inclusion criteria are as follows:

1. Male or female patients aged 18–75 y
2. Negative pregnancy test for all women of child-bearing potential, or surgically sterilized before screening, or postmenopausal for at least 1 y
3. Acute MI defined as:
   - Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with ≥1 of the following:
     1. Ischemic symptoms; (2) development of pathological Q waves on the ECG; (3) ECG changes indicative of ischemia (ST-segment-elevation or depression)
   - First anterior or inferolateral STEMI or Q wave MI
   - Regional wall motion score index (≥2 of 16 akinetic segments)
4. One or more of the following:
   - LV EF >20% and <45% measured and calculated by 2-dimensional echocardiographic measurement
   - Biomarkers: peak CK >2000 IU
   - Infarct size >25% as measured by MRI
5. Successful revascularization with PCI within 7 days of the index MI
6. At the time of device application, the patient must have a patent IRA and TIMI flow grade ≥3

**Table 1. Patient Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
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</tr>
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<tbody>
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**Exclusion criteria**

1. History of CHF, Class I to Class IV, as per NYHA criteria
2. History of prior LV dysfunction
3. At time of device application of study device—Killip III-IV or HR >100 bpm
4. Patient with pacemaker
5. Prior CABG
6. Prior MI
7. History of stroke
8. Significant valvular disease (moderate or severe)
9. Patient is a candidate for CABG or PCI on non-IRA
10. Patient is being considered for CRT within the next 30 days
11. Renal insufficiency (eGFR<60)
12. Chronic liver disease (liver enzymes >3 times upper limit of normal)
13. Life expectancy <12 mo
14. Current participation in another clinical trial or participation in another trial within the last 6 mo
15. Any contraindication to coronary angiography MRI or PCI procedures
16. Patient taking anticoagulation medication before MI
17. Pregnant or lactating women; pregnancy confirmed by pregnancy test
18. Patients with a reasonable likelihood for noncompliance with the protocol
19. Any other reason that, in the investigator’s opinion, prohibits the inclusion of the patient into the study

CABG indicates coronary artery by-pass grafting; CHF, congestive heart failure; CK-MB, creatine kinase, muscle and brain; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HR, heart rate; IRA, infarct-related artery; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRI, magnetic resonance imaging; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.
and exclusion criteria are provided in Table 1. All patients had coronary angiography with PCI, including stent implantation in the infarct-related artery (IRA).

**Study Procedures and Device Deployment**

After determining eligibility for the trial and obtaining informed consent, biomarkers (creatine kinase; creatine kinase, muscle and brain; and N-terminal probrain natriuretic peptide [NT-proBNP]) were obtained. Echocardiography and coronary angiography were obtained at baseline. In a second procedure occurring within 7 days of the infarct, 2 mL of IK-5001 (BioLineRx, Jerusalem, Israel) was deployed by injection into the free-flowing IRA over <30 seconds. The infusion catheter was placed immediately distal to the previously deployed stent. Coronary angiography was repeated 3 minutes after IK-5001 implantation, and biomarkers (including creatine kinase and creatine kinase, muscle and brain) were obtained at 8, 16, and 24 hours after device deployment.

Individual cases were carefully reviewed by an independent safety monitoring board (ISMB), after the first 2 treated patients, and then after the next 3 treated patients, and then after treatment of each group of 5 patients. After each review, the ISMB had an option to recommend to continue enrollment, discontinue enrollment, or modify study procedures. At each review, the ISMB recommended that the study continue enrollment.

**Echocardiography**

LV remodeling and function were assessed by 2-dimensional echocardiography, before deployment and then at days 30, 90, and 180, using a predefined protocol. All echocardiograms were interpreted by a central laboratory (Biomedical Systems, St. Louis, MO).

The echocardiographic studies were performed according to a strict, detailed protocol provided by the core echocardiography laboratory. To assure the quality of the tests, a qualified cardiologist/sonographer performed all ultrasound examinations. Before performing echocardiograms on study patients, any participating cardiologist was certified by Biomedical Systems, Echo Core Laboratory. All participating sonographers or cardiologists were required to submit a test echocardiogram on a healthy nonstudy participant for the purpose of site certification.

Echocardiography required the following views: parasternal long-axis, parasternal short-axis, apical 4-chamber, apical 5-chamber, apical 2-chamber, apical long-axis (3-chamber), and subcostal.

To achieve reproducibility during image acquisition, it was strongly advised that the same ultrasound system and, if possible, the same cardiologist be used for each patient for all subsequent visits. If deemed necessary, an approved intravenous ultrasonograph contrast agent was used to opacify the LV for the purpose of evaluating the ejection fraction. The cardiologist at the institution performing the echocardiograms was responsible for ensuring that the use of such agents was in accordance with local guidelines.

The protocol required that at least 3 beats of each image using harmonic imaging at held expiration were acquired, and excessive respiration and transducer movement during image acquisition were avoided. Additional views were at the discretion of the cardiologist obtaining the information. Doppler and M-mode images were shown on a frozen spectral display at held expiration (≥3 beats) with the 2-dimensional image sample site in view.

To study the changes in LV regional wall motion, the standardized 16-segment model was used. The wall motion score was determined by the core laboratory as: 1=normal, 2=hypokinesis, 3=akinesis, 4=dyskinesis, and 5=aneurysm. Segmental wall motion score, in the infarct zone, was assessed by the assignment of the score, in the infarct zone, was assessed by the assignment of the segmental wall motion score. The core laboratory was responsible for the quality assurance of the echocardiographic images.

<table>
<thead>
<tr>
<th>Table 2. Primary and Secondary End Points</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary end points</strong></td>
</tr>
<tr>
<td>Occurrence of all adverse events</td>
</tr>
<tr>
<td>Symptomatic heart failure</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Stroke death</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
</tr>
<tr>
<td>Change from baseline in LV dimensions</td>
</tr>
<tr>
<td>Change from baseline in regional and global wall motion score</td>
</tr>
<tr>
<td>Change from baseline in ejection fraction</td>
</tr>
<tr>
<td>Cardiac rupture</td>
</tr>
<tr>
<td>NT-proBNP</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; and NT-proBNP, N-terminal probrain natriuretic peptide.

**Study End Points**

The primary and secondary end points of the trial are listed in Table 2. Follow-up visits were arranged at 30, 90, and 180 days after IK-5001 deployment. At these visits, NT-proBNP was measured and an echocardiogram was done, as well as 24-hour Holter monitoring. Adverse events and serious adverse events were registered and laboratory evaluation was obtained.

After the initial 180-day follow-up visit, patients were followed for 12, 24, 36, 48, and 60 months after deployment. Each of these visits included questioning for adverse and serious adverse events and laboratory evaluation. This report lists the results following the primary and secondary end points at 180 days after device deployment. The long-term results subsequent to the 180-day visit were pending at the time of this report.

Follow-up data, abnormal laboratory findings, and clinical events were carefully examined and interpreted by the ISMB.

**Statistical Analysis**

Statistical analysis was performed with GraphPad Prism version 6.00 for Mac OS X (GraphPad Software, La Jolla, CA, USA, www.graphpad.com). Descriptive data of continuous variables were analyzed using mean, median, and standard deviation. Descriptive analysis of categorical variables was performed using frequency counts and percentages. Unless otherwise specified, the intention-to-treat population was analyzed and patients who dropped out of the study were not replaced; all information obtained from them was included in the analysis. Comparisons of preimplantation with follow-up values were performed by ANOVA test, or if normality was not found, by the nonparametric approach of Kruskal-Wallis, followed by the Dunnett multiple comparisons test.

**Results**

**Safety Data Immediately After Implant**

A total of 27 patients (mean age 54±9 years) after an ST-segment–elevation myocardial infarction (STEMI) were treated during the course of this trial (Table 3). Most patients were male (n=24), had experienced an anterior MI (n=19), and had been admitted in Killip Class-I (n=23; Table 3). The time from symptom onset to primary PCI ranged from 0.6 to 84.7 hours (mean, 9.9±16.9 hours; median, 3.8 hours).

All treated patients tolerated device deployment well. The Thrombolysis in Myocardial Infarction (TIMI) flow grade and TIMI myocardial perfusion grade for each patient before and immediately after IK-5001 deployment were scored by...
Table 3. Patient Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total No. of Patients (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, years</td>
<td>54±9</td>
</tr>
<tr>
<td>Male, n</td>
<td>24</td>
</tr>
<tr>
<td>Caucasian, n</td>
<td>26</td>
</tr>
<tr>
<td>Asian, n</td>
<td>1</td>
</tr>
<tr>
<td>Body mass index, mean±SD</td>
<td>30±8</td>
</tr>
<tr>
<td>Time from AMI to implant, median, days</td>
<td>5</td>
</tr>
<tr>
<td>Peak CK, mean±SD</td>
<td>3183±1490</td>
</tr>
<tr>
<td>Left anterior descending IRA, n</td>
<td>19</td>
</tr>
<tr>
<td>Left circumflex IRA, n</td>
<td>5</td>
</tr>
<tr>
<td>Right coronary IRA, n</td>
<td>3</td>
</tr>
<tr>
<td>Killip Class I, n</td>
<td>23</td>
</tr>
<tr>
<td>Killip Class II, n</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes mellitus, n</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>14</td>
</tr>
<tr>
<td>Dyslipidemia, n</td>
<td>18</td>
</tr>
<tr>
<td>Currently smoking, n</td>
<td>10</td>
</tr>
<tr>
<td>Previous smoking, n</td>
<td>11</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; CK, creatine kinase; IRA, infarct-related artery; and SD, standard deviation.

Table 4. Thrombolysis in Myocardial Infarction Flow Grade and TIMI Myocardial Perfusion Grade Before and After Device Deployment

<table>
<thead>
<tr>
<th>TIMI flow grade*</th>
<th>Immediately Before Deployment No. of Patients</th>
<th>Immediately (3 min) After Deployment No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TIMI myocardial perfusion grade (TMG)†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>18</td>
</tr>
</tbody>
</table>

TIMI indicates Thrombolysis in Myocardial Infarction.

*TIMI flow grade as per central laboratory determination (PERFUSE Laboratory, Boston, MA). Of the 27 patients in the study, only 26 had data quality sufficient to determine TIMI flow grade by the core angiographic laboratory.

†For TMG, only 10 predployment angiograms were sufficient for central laboratory interpretation and only 22 of the postdeployment angiograms were judged sufficient for definitive interpretation.

Figure 1. Deployment of the IK-5001 device did not produce additional myocardial injury as indicated by serial measures of creatine kinase, muscle and brain (CK-MB).

Adverse Events

No adverse events were related to treatment with the IK-5001 device, as judged by the independent ISMB. Of the 27 treated patients, 21 reported ≥1 adverse event (Table 5). Eight patients experienced ≥1 treatment-emergent serious adverse event. One event, a single episode of syncope, which occurred 172 days after device deployment, was judged as possibly related to the device. There were no serious adverse events with the

Table 5. Cardiac Adverse Events of Special Interest and Treatment-Emergent Adverse Events Reported by ≥2 Patients by Organ Disorder

<table>
<thead>
<tr>
<th>Cardiac adverse events of special interest</th>
<th>No. of Patients (n=27) With at Least 1 Report Within 180 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular hospitalization</td>
<td>5</td>
</tr>
<tr>
<td>Recurrent myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1†</td>
</tr>
<tr>
<td>Second-degree heart block type II (Mobitz II)</td>
<td>1†</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Symptomatic heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>0</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs reported by ≥2 patients by organ disorder</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>9</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>4</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>3</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>3</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>2</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>2</td>
</tr>
</tbody>
</table>

TEAEs indicates treatment-emergent adverse events.

*One event, syncope occurring 172 days following implant was judged to be possibly related to the device.

†Occurred 27 days following implant; not reported as a serious adverse event.

‡Occurred 32 days following implant; not reported as a serious adverse event.
device (Table 5). The most common treatment-emergent adverse events within 180 days of device deployment were chest pain (5 patients), angina pectoris (2 patients), elevated creatine kinase (2 patients), epistaxis (2 patients), nausea (2 patients), and headache (2 patients). None of these were judged to be related to the device.

LV Remodeling and Function
In the 6-month period after a large MI, and similar to preclinical findings, the patients in this study preserved their LV end-diastolic volume index, LV end-systolic volume index, and LV ejection fraction (LVEF; Figures 2 and 3). Analysis of the regional wall motion score of the LV segments supplied by the IRA18 showed a mild recovery of the infarcted segments (Figure 4). However, because this was a single-group, uncontrolled study, it was not possible to compare these values or the change from baseline with a control group.

Minnesota Living With Heart Failure Questionnaire
The majority of study patients completed the Minnesota Living with Heart Failure Questionnaire. The average quality of life was improved during the 180-day follow-up period (Table 6). However, these findings should be interpreted with caution because this was an uncontrolled, single-arm study.

Arrhythmias
Continuous 24-hour ECG monitoring was performed on the day of deployment and at 30, 90, and 180 days after deployment. No significant ventricular arrhythmias were observed in any of these recordings. However, rare supraventricular bradyarrhythmias were observed: second-degree heart block was seen in 1 patient at day 30 and symptomatic bradycardia in another patient at day 90. All other recordings were unremarkable.

NT-proBNP
NT-proBNP is an accepted biomarker of worsening heart failure. Initial determination of NT-proBNP during the peri-STEMI period showed an expected elevation of this biomarker. During the ensuing 6 months after the STEMI and implantation of the IK-5001 device, the NT-proBNP steadily decreased (Table 7).

Discussion
This report describes the results of a pilot study of the first 27 patients treated with a novel self-assembling, self-disassembling temporary bioabsorbable cardiac scaffold. We have shown that intracoronary deployment of an IK-5001 scaffold within the first week after STEMI seems feasible and well tolerated.

A major advantage of the present approach is that it is performed in the catheterization laboratory, via percutaneous radial artery access, under local anesthesia. Thus, our approach avoids the need for surgical procedure performed under general anesthesia. Furthermore, the selective intracoronary delivery of the scaffold is relatively simple and does not require a unique delivery device or complex imaging system.

When injected into the reperfused IRA, the hydrogel is presumed to deposit within the infarcted tissue to provide a temporary myocardial extracellular matrix and biomechanical support after a large MI.9,10 Based on previous animal experiments, this temporary scaffold then replaces the damaged extracellular matrix, thereby reducing wall thinning and strain. The device attenuates the ensuing LV dilation, infarct expansion, and impaired myocardial function after large MI.9,10
considered biocompatible and biologically inert.17,19–22 Fourth, alginate has been used widely in the food industry, used medically to encapsulate cells for tissue engineering for the treatment of ischaemic heart disease.18 This finding is not unexpected because IK-5001 is biocompatible with reperfused myocardium. This finding is not unexpected because IK-5001 remains liquid within the vasculature and undergoes phase transition to a hydrogel only once it has entered the extracellular space of the infarcted myocardium with its elevated free calcium levels. Third, the absence of deployment-related or 180-day changes in ECG or cardiac biomarkers indicates that there is progressive dilation of the LV cavity to 12 months after infarction.1,2 This dilation of the LV cavity during the 6 months post-STEMI was feasible and well tolerated. Second, this study in humans confirms previous experimental animal data, indicating that intracoronary injection of 2 mL of IK-5001 within the first 7 days post-STEMI was feasible and not a must because some centers did not have on-site MRI, and other patients were not eligible for MRI study because of overweight, claustrophobia, or an implanted device. The primary goal of this pilot study was feasibility. MRI was considered to be the gold standard for the evaluation of cardiac remodeling and function. Furthermore, MRI could provide valuable data on infarct size and microcirculation. However, the primary goal of this pilot study was feasibility. MRI was not an obligatory criterion, enrolling patients with LVEF >45% may have created a bias toward a low-risk population. The source for this bias was because of lower estimation of the baseline LVEF by the local sonographers compared with that estimated by the core laboratory sonographers.

Fourth, patients who are treated by PCI within 6 hours after symptom onset, and those with well-developed functional collaterals, are likely to experience small infarcts with mild LV remodeling and dysfunction. These low-risk patients should be excluded from future studies that aim toward high-risk MI patients.

Fifth, the patients in the present pilot study were not evaluated by magnetic resonance imaging (MRI), which is considered to be the gold standard for the evaluation of cardiac remodeling and function. Furthermore, MRI could provide valuable data on infarct size and microcirculation. However, the primary goal of this pilot study was feasibility. MRI was not a must because some centers did not have on-site MRI, and other patients were not eligible for MRI study because of overweight, claustrophobia, or an implanted device. Another limitation is that coronary flow, reserve, and microvascular resistance were not measured. Invasive evaluation before and after device deployment could add valuable information on the effect of the device on coronary flow and microvascular resistance.

Finally, because this was a first-in-man pilot study, the study population was small and infrequent adverse events may not have been observed because of the limited number of patients. Larger subsequent studies are required to confirm the safety and efficacy of the device.

This first-in-man safety study addresses several important questions. First, that the intracoronary injection of 2 mL of IK-5001 within the first 7 days post-STEMI was feasible and well tolerated. Second, this study in humans confirms previous experimental animal data, indicating that intracoronary injection of IK-5001 into a free-flowing IRA does not compromise intracoronary or myocardial microvascular blood flow.1 These results provide critical support for the proposition that IK-5001 is biocompatible with reperfused infarcted myocardium. This finding is not unexpected because alginate has been used widely in the food industry, used medically as a wound dressing and a bone filler, and is generally considered biocompatible and biologically inert.17,19–22 Fourth, the adverse event profile from these 27 patients with STEMI was consistent with a post-MI population and revealed no unexpected adverse events that were attributed by the ISMB to IK-5001 device deployment. Nevertheless, the patient population was small in this first-in-man study, and there was no control group for comparison.

Although this study was designed to determine the feasibility of this device in this first-in-man study, it also provided limited efficacy data. Prior studies on extensive MI demonstrate that there is progressive dilation of the LV during the 6 to 12 months after infarction.12 This dilation of the LV cavity is accompanied by progressive deterioration in cardiac function as determined by LVEF. Although interpretation of the echocardiographic data in this study is limited by the lack of a control group, it is encouraging that similar to preclinical experiments, little dilation of the LV cavity was observed and LVEF was preserved during the 6-month period after a moderate-to-large MI. Whether this represents an improvement in the reduction or prevention of LV remodeling after MI will need to be determined in subsequent randomized, blinded, and controlled studies using this device in this population.

### Study Limitations

The primary limitation of this pilot study was its lack of a randomized control group for comparison. Without such a control group, the safety and efficacy data should be interpreted with caution, by comparing with expected results from the current standard of care. However, this technique is limited and rigorous comparison to a control group cannot be made.

The second limitation was the lack of blinding inherent in a single-arm, open-label study. Because all patients were aware that they were receiving an investigational device, symptoms and complaints may have been influenced by the placebo effect. This is especially true of adverse event reports and symptoms, although it is unlikely that a placebo effect influenced LV size and function.

Third, data analysis by the core laboratory revealed that the pilot study included patients with baseline LVEF >45% (n=18). Although LVEF was not an obligatory criterion, enrolling patients with LVEF >45% may have created a bias toward a low-risk population. The source for this bias was because of lower estimation of the baseline LVEF by the local sonographers compared with that estimated by the core laboratory sonographers.

The primary limitation of this pilot study was its lack of a randomized control group for comparison. Without such a control group, the safety and efficacy data should be interpreted with caution, by comparing with expected results from the current standard of care. However, this technique is limited and rigorous comparison to a control group cannot be made.

The second limitation was the lack of blinding inherent in a single-arm, open-label study. Because all patients were aware that they were receiving an investigational device, symptoms and complaints may have been influenced by the placebo effect. This is especially true of adverse event reports and symptoms, although it is unlikely that a placebo effect influenced LV size and function.

Fourth, patients who are treated by PCI within 6 hours after symptom onset, and those with well-developed functional collaterals, are likely to experience small infarcts with mild LV remodeling and dysfunction. These low-risk patients should be excluded from future studies that aim toward high-risk MI patients.

Fifth, the patients in the present pilot study were not evaluated by magnetic resonance imaging (MRI), which is considered to be the gold standard for the evaluation of cardiac remodeling and function. Furthermore, MRI could provide valuable data on infarct size and microcirculation. However, the primary goal of this pilot study was feasibility. MRI was not a must because some centers did not have on-site MRI, and other patients were not eligible for MRI study because of overweight, claustrophobia, or an implanted device.

Another limitation is that coronary flow, reserve, and microvascular resistance were not measured. Invasive evaluation before and after device deployment could add valuable information on the effect of the device on coronary flow and microvascular resistance.

Finally, because this was a first-in-man pilot study, the study population was small and infrequent adverse events may not have been observed because of the limited number of patients. Larger subsequent studies are required to confirm the safety and efficacy of the device.

### Table 6. Minnesota Living With Heart Failure Total Score at Days 30, 90, and 180 After IK-5001 Deployment

<table>
<thead>
<tr>
<th>Days After IK-5001 Deployment (No. of Patients)</th>
<th>Minnesota Living With Heart Failure Total Score (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 30 (n=22)</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>Day 90 (n=21)</td>
<td>18 ± 4*</td>
</tr>
<tr>
<td>Day 180 (n=25)</td>
<td>16 ± 3†</td>
</tr>
</tbody>
</table>

Differences among mean scores are significant (P<0.0001) by ANOVA. SD indicates standard deviation.

*P<0.05 compared with day 30, by the Dunnett multiple comparison test.
†P<0.05 compared with day 30, by the Dunnett multiple comparison test.

### Table 7. NT-proBNP Levels During 6 Months After the STEMI and Implantation of the IK-5001 Device

<table>
<thead>
<tr>
<th>Time</th>
<th>Preimplant (n=23)</th>
<th>Discharge (n=22)</th>
<th>30 Days (n=20)</th>
<th>90 Days (n=23*)</th>
<th>180 Days (n=26†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (mean±SD)</td>
<td>2977±5392</td>
<td>1313±1434</td>
<td>1064±1138</td>
<td>619±672</td>
<td>566±847</td>
</tr>
</tbody>
</table>

Differences among mean values are significant (P<0.0001) by Kruskal-Wallis test. NT-proBNP indicates N-terminal probrain natriuretic peptide; SD, standard deviation; and STEMI, ST-segment–elevation myocardial infarction.

*P<0.05 compared with preimplant, by the Dunnett multiple comparison test.
†P<0.05 compared with preimplant, by the Dunnett multiple comparison test.
Summary Implications and Future Research

Selective intracoronary injection of alginate hydrogel solution in survivors of a first MI is feasible and well tolerated. This first-in-man study provides initial proof of the concept that a novel catheter-based strategy can be used after MI. Based on positive preclinical data9,10 and the encouraging findings of the present pilot study, we have designed and launched a pivotal trial. The PRESERVATION-1: IK-5001 for the prevention of remodeling of the ventricle and congestive heart failure after acute MI (ClinicalTrials.gov Identifier: NCT01226563) is an ongoing multicenter, randomized, controlled, double-blind trial, aimed to determine the safety and effectiveness of the IK-5001 device for the prevention of ventricular remodeling and congestive heart failure when administered to subjects who had successful PCI with stent placement after STEMI. The ability to deliver biomaterial into the infarct by intracoronary injection could revolutionize patient treatment after MI and prevent LV remodeling, mechanical complications, heart failure, and death.

Acknowledgments

Editorial support for preparation of this manuscript was provided by Peloton Advantage, LLC, Parsippany, New Jersey, USA, and funded by Ikaria, Inc.

Sources of Funding

The study was sponsored by BioLineRx, Jerusalem, Israel. The product (IK-5001) was in-licensed from BioLineRx in 2009 by Ikaria (spun-out as Bellerophon Therapeutics LLC).

Disclosures

Dr Linke has received grant/research support from Claret Medical, Inc., and Medtronic, Inc. He has been a consultant for Medtronic, Inc. and St. Jude Medical, Inc., and has received honoraria from Boston Scientific, Edwards Lifesciences Corporation, Medtronic, Inc., and St. Jude Medical, Inc. Dr Sisulbeck is a stock shareholder with St. Jude Medical, Inc., and has received honoraria from Boston Scientific, Medtronic, Inc., and Sorin Group. Dr Leor applied for a patent on injectable alginate for myocardial repair via Ben-Gurion University and was a medical consultant for BioLine Innovations, Jerusalem, Israel. The other authors report no conflicts.

References

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Circ Cardiovasc Interv. 2014;7:806-812; originally published online October 28, 2014; doi: 10.1161/CIRCINTERVENTIONS.114.001478
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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