15 YEARS OF EXPANDING MITRACLIP EXPERIENCE

FRANCESCO MAISANO MD, FESC
• CONSULTANT FOR ABBOTT
• EDUCATIONAL GRANTS FROM ABBOTT
Evolution of the Alfieri technique: 
From surgery to catheter based
2008, One of the first EVEREST slides

EVEREST Registry: Number of Clips

(N = 104)

- 0 Clips: 11
- 1 Clip: 62
- 2 Clips: 31

2 patients underwent re-intervention to place a 2nd Clip
First mitral repair device tested against surgery

**EVEREST II Randomized Clinical Trial**

Study Design

- 279 Patients enrolled at 37 sites
- Significant MR (3+ to 4+)
- Specific Anatomical Criteria
- Randomized 2:1

**Device Group**
- MitraClip System
  - N=184

**Control Group**
- Surgical Repair or Replacement
  - N=95

**Echocardiography Core Lab and Clinical Follow-Up:**
- Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years.
Percutaneous Mitral Repair With the MitraClip System

Safety and Midterm Durability in the Initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) Cohort

Ted Feldman, MD,* Shibli Kar, MD,† Michael Rinaldi, MD,‡ Peter Fai, MD,§
James Herrnoller, MD,¶ Richard Smalling, MD, PhD,† Patrick L. Whitlow, MD,#
William Grey, MD,** Reginald Low, MD,†† Howard C. Herrmann, MD,¶¶ Scott Lim, MD,¶¶¶
Elyse Foster, MD,¶¶ Donald Glower, MD,¶¶¶ for the EVEREST Investigators

Evans, Illinois; Las Vegas, Sacramento, and San Francisco, California; Charlotte and Durham,
North Carolina; Houston, Louisiana; Indianapolis, Indiana; Houston, Texas; Cleveland, Ohio;
New York, New York; Philadelphia, Pennsylvania; and Charlotteville, Virginia

Objectives
We undertook a prospective multicenter single-arm study to evaluate the feasibility, safety, and efficacy of the MitraClip system. (Edwards Inc., Menlo Park, California)

Background
Mitral valve repair for mitral regurgitation (MR) has been performed by the use of a surgically created double orifice. Percutaneous repair based on this surgical approach has been developed by use of the Endovascular MitraClip device to secure the mitral leaflets.

Methods
Patients with 3 to 4+ MR were selected in accordance with the American Heart Association/American College of Cardiology guidelines for intervention and 2D echocardiographic laboratory.

Results
A total of 107 patients were treated. Ten (9%) had a major adverse event, including 2 reoperations for death. Freedom from clip detachment was 100%. Partial clip detachment occurred in 10 (9%) patients. Overall, 79 of 107 (74%) patients achieved acute procedural success, and 55 (54%) were discharged with MR of ≤1+. Thirty-two patients (30%) had mitral valve surgery during the 3.2 years after clip procedures. Mean septal thickness was 18.4 ± 5.2 mm. The mean septal thickness at the time of the mitral valve surgery was 14.2 ± 5.2 mm. The mean septal thickness at the time of the mitral valve surgery was 14.2 ± 5.2 mm. The mean septal thickness at the time of the mitral valve surgery was 14.2 ± 5.2 mm. The mean septal thickness at the time of the mitral valve surgery was 14.2 ± 5.2 mm. The mean septal thickness at the time of the mitral valve surgery was 14.2 ± 5.2 mm.

Conclusions
Percutaneous repair with the MitraClip system can be accomplished with low rates of morbidity and mortality and with acceptable MR reduction to ≤2+. In the majority of patients, and with sustained freedom from death, surgery, or re-current MR in a substantial proportion (EVEREST, NCT00500339; EVEREST II, NCT00906274). (J Am Coll Cardiol 2009;64:886-946 © 2009 by the American College of Cardiology Foundation)
MitraClip (N=178)
MR ≤ 2+ at 1 and 5 Years

Surgery (N=80)
MR ≤ 2+ at 1 and 5 Years


N = survivors with paired data; p-values for descriptive purposes only
FMR is the main indication in EU, mostly beyond EVEREST criteria

77% of pts do not meet EVEREST II anatomical inclusion criteria

Percutaneous Mitral Repair With the MitraClip System
Safety and Midterm Durability in the Initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) Cohort

Ted Feldman, MD,* Seibul Kua, MD,** Michael Ronald, MD,‡ Peter Fall, MD,§ James Hermsmeyer, MD,¶ Richard Smalling, MD,§ Patrick L. Whibley, MD,¶ William Gray, MD,¶ Reginald Low, MD,¶ Howard C. Herrmann, MD,¶ Scott Lim, MD,¶* Elyse Foster, MD,¶ Donald Glower, MD,¶† for the EVEREST Investigators
Evanston, Illinois; Los Angeles, Sacramento, and San Francisco, California; Charlotte and Durham, North Carolina; Houston, Louisiana; Indianapolis, Indiana; Houston, Texas; Cleveland, Ohio; New York, New York; Philadelphia, Pennsylvania; and Charlottesville, Virginia

Objectives
We undertook a prospective multicenter single-arm study to evaluate the feasibility, safety, and efficacy of the MitraClip system. (Evaive Inc., Menlo Park, California)

Background
Mitrail valve repair for mitral regurgitation offers: Percutaneous repair favors the use of devices that conserve the mitral leaflets.

Methods
Patients with 3 to 6+ MR were enrolled. Cardiology guidelines for intervention

Results
A total of 207 patients were treated. From the clip implantation, 100% of the patients achieved successful procedures or (30%) had mitral valve surgery during were successful. Thus, surgical options for mild, moderate, severe, and very severe mitral regurgitation, from death, mild valve surgery, death was 95.0%, 94.0%, and 9 at 1, 2, and 3 years, respectively. The

Conclusions
Percutaneous repair with the MitraClip system, with acute NR reduction to ≤ 2 + in more than 75% of cases, was associated with a significantly higher procedural success rate and lower rates of death and stroke compared to conventional surgery.
MITRACLIP: The only TMVr therapy with extensive clinical and real-world experience

- +15 YEARS OF EVIDENCE BUILDING*
- +1,000 PUBLISHED ARTICLES*
- +70,000 PATIENTS TREATED WORLDWIDE*
- +1,000 CENTERS IN NEARLY 50 COUNTRIES WORLDWIDE*

*Data on file at Abbott
MITRACLIP CLINICAL TRIAL EXPERIENCE

- First Case
- EVEREST I Feasibility (N=55)
- EVEREST II Roll-In & RCT (N=339)
- EVEREST II HRR (N=78)
- REALISM (N=965)
- RESHAPE-HF (N=42)
- PAS-1 (N=1,998)
- PAS-2 (N=554)
- ACCESS-EUROPE Phase I-II (N=853)
- MITRACLIP ANZ (N=78)
- COAPT (N=614 Randomized)
- COAPT CAS (N=31)
- Up to 800 to be enrolled
- MITRACLIP JAPAN (N=30)
- TRILUMINATE (N=11)

Legend:
- Study closed
- Enrolment complete, follow-up through 5 years ongoing
- Enrolling

Current as of February 2018
The Most Studied TMVr Therapy

<table>
<thead>
<tr>
<th>MITRACLIP STUDIES*</th>
<th>N</th>
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<tbody>
<tr>
<td>EVEREST I (feasibility study)</td>
<td>55</td>
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<tr>
<td>EVEREST II^*</td>
<td>279</td>
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<tr>
<td>EVEREST HRR†</td>
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<tr>
<td>EVEREST II REALISM (continued access)</td>
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<tr>
<td>ACCESS-EU I †</td>
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<tr>
<td>ACCESS-EU II †</td>
<td>289</td>
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<td>TRAMI†</td>
<td>1,350</td>
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<td>GRASP†</td>
<td>304</td>
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<tr>
<td>MITRASWISS†</td>
<td>265</td>
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<td>SENTINEL †</td>
<td>628</td>
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<tr>
<td>MARS†</td>
<td>145</td>
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<tr>
<td>ANZ MITRACLIP Registry†</td>
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<td>MitraClip Japan Study†</td>
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<tr>
<td>TVT Registry†</td>
<td>2,942</td>
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<tr>
<td>MITRA-FR†</td>
<td>307 ‡</td>
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<tr>
<td>COAPT*</td>
<td>614</td>
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</table>

*Inclusive of principal studies with concluded enrolled up to August 2018.
^Single-arm study
†Randomized controlled trial
‡Number of patients randomized
Consistent durable results across 5 studies\(^1\text{-}^5\) in terms of:

- Safety
- MR reduction
- NYHA improvement
- LV remodeling

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<table>
<thead>
<tr>
<th></th>
<th>MITRA-FR</th>
<th>COAPT</th>
<th>RESHAPE-HF2*</th>
<th>MATTERHORN*</th>
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<tbody>
<tr>
<td><strong>Study sponsor</strong></td>
<td>Hospices Civils de Lyon sponsored, French government funded</td>
<td>Abbott sponsored and funded</td>
<td>Investigator sponsored study</td>
<td>Investigator sponsored study</td>
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<tr>
<td><strong>Purpose of the study</strong></td>
<td>Generate clinical evidence to support activities, including French reimbursement for severe FMR</td>
<td>Regulatory approval for moderate-to-severe or severe secondary MR</td>
<td>Additional clinical data</td>
<td>Additional clinical data</td>
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<tr>
<td><strong>Patients</strong></td>
<td>307‡</td>
<td>614</td>
<td>800</td>
<td>210</td>
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<tr>
<td><strong>Control arm</strong></td>
<td>GDMT ± CRT</td>
<td>GDMT ± CRT</td>
<td>GDMT ± CRT</td>
<td>MV surgery</td>
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<tr>
<td><strong>Primary endpoint</strong></td>
<td>All-cause death or unplanned heart failure rehospitalization at 12 months (time-to 1st event analysis)</td>
<td>Recurrent HF hospitalizations through 24 months, analyzed when the last subject completes 12-month follow-up</td>
<td>Death or recurrent HF hospitalization at 12 months (time-to 1st event analysis)</td>
<td>Death, HF hospitalization, reintervention, assist device implantation or stroke</td>
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<td><strong>Total follow-up</strong></td>
<td>2 years</td>
<td>5 years</td>
<td>1 year</td>
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</table>

*Number of patients randomized  *Enrollment not complete
Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation


ABSTRACT

BACKGROUND

In patients who have chronic heart failure with reduced left ventricular ejection fraction, severe secondary mitral valve regurgitation is associated with a poor prognosis. Whether percutaneous mitral valve repair improves clinical outcomes in this patient population remains unknown.

METHODS

We randomly assigned patients who had severe secondary mitral valve regurgitation identified as an off-label indication of the MitraClip system to percutaneous mitral valve repair or to medical therapy alone. The primary efficacy outcome was a composite of death from any cause or unplanned hospitalization for heart failure at 12 months.

RESULTS

In 12 months, the rate of the primary outcome was 54.8% (66 of 121 patients) in the intervention group and 75.2% (79 of 103 patients) in the control group (hazard ratio, 1.35; 95% confidence interval, 1.07 to 1.72; P = 0.009). The rate of death from heart failure was 29.6% (37 of 121 patients) in the intervention group and 21.8% (23 of 103 patients) in the control group (hazard ratio, 1.33; 95% confidence interval, 0.87 to 1.99; P = 0.19). The rate of unplanned hospitalization for heart failure was 55.6% (68 of 121 patients) in the intervention group and 59.0% (60 of 103 patients) in the control group (hazard ratio, 1.09; 95% confidence interval, 0.83 to 1.46; P = 0.53).

CONCLUSIONS

Among patients with severe secondary mitral regurgitation, the rate of death or unplanned hospitalization for heart failure at 1 year did not differ between patients who underwent percutaneous mitral valve repair as add-on therapy and those who received medical therapy alone. (Funded by the Finnish Agency of Health and Research National Foundation and Jitkari Vardi-Black; MitraClip Investigators.)
Hope is hard to kill....
MitraClip® NT

- Leaflet grasping and steering enhancements

MitraClip NTR & MitraClip XTR

- Improved grasping, increased coaptation surface area, complex valve anatomy
- Customized repair with 2 Clip sizes
- Enhanced steering accuracy and ease-of-use

MitraClip GEN 4*

- Improved ease-of-use
- Improved leaflet grasping
- Further increased coaptation surface area with multiple Clip sizes

TRICUSPID Clip†

- Designed for the right atrium
- Designed to restore coaptation of TV leaflets
- Designed to access all areas of the tricuspid valve

MitraClip NTR & MitraClip XTR

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GEN 2 2016

GEN 3 2018

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GEN 5

- Enhanced Steering accuracy
- Improved ease-of-use

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*Currently in development at Abbott. Not currently for sale. Image for illustration purposes only.
†Tricuspid: Exclusively for clinical investigations. Currently in development at Abbott and being evaluated in clinical trials and intended for use by or under the direction of a physician. Not available for sale.
CREATING New Evidence to Support the 3rd Generation of MitraClip

The EXPAND observational study will generate current, marketable clinical evidence for MitraClip® NTR and MitraClip XTR

- Enrollment goal: 1000 patients
- 60+ centers across EMEA and US
- CEC adjudicated for major adverse events
- Two Clip sizes to expand treatment options
- The new Clip Delivery System is designed to be more precise and predictable

*This figure reflects the additional grasping width at 120° achieved with the MitraClip XTR Clip

MitraRepair: Expand Observational Study

The EXPAND observational study will generate current, marketable clinical evidence for MitraClip® NTR and MitraClip XTR

- Enrollment goal: 1000 patients
- 60+ centers across EMEA and US
- CEC adjudicated for major adverse events
- Independent echo core lab
- First patient in: April 2018
EXPAND STUDY DESIGN

- **Design:** Prospective, Multi-Center, Single Arm, International, Post Market, Observational Study

- **Patients:** Up to 1,000 consecutive, eligible subjects at a maximum of 60 sites in Europe and the US treated with MitraClip NTR or MitraClip XTR, who provide informed consent to participate in study
  - A subset of evaluable echocardiograms will be selected for a more detailed assessment by an independent core lab

- **Clinical Visits:** 30 days and 12 Months

- **Echocardiogram (TTE):** Baseline, Discharge, 30 days & 12 Months

- **Phone Call:** 6 Months

- **Inclusion/Exclusion Criteria:**

<table>
<thead>
<tr>
<th>INCLUSION</th>
<th>EXCLUSION</th>
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<tbody>
<tr>
<td>1. Subjects with symptomatic MR (≥3+)</td>
<td>1. Subjects participating in another clinical study that may impact the follow-up or results of this study.</td>
</tr>
<tr>
<td>2. Subjects who give consent for study participation</td>
<td></td>
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<tr>
<td>3. Subjects eligible to receive the MitraClip per the current approved indications for use.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Enrolled Subjects</th>
<th>Europe</th>
<th>US</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>66</td>
<td>15</td>
<td>81</td>
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</tbody>
</table>
Transseptal Puncture
Transseptal Puncture
• Longer arms = more leaflet insertion
• Longer arms = more efficient in Barlow’s
• Longer arms = easier grasping
• Longer arms = reduced need for second clip
Device selection

- Longer arms = more leaflet insertion
- Longer arms = more efficient in Barlow’s
- Longer arms = easier grasping
- Longer arms = reduced need for second clip
- Longer arms = risk of leaflet distortion (?)
- Longer arms = risk of leaflet perforation (?)
- Longer arms = higher risk of clip entanglement (?)

Clip Arms at 120 degrees

NTR

XTR

17 mm

22 mm
Driving a F1 is not like driving a regular car.
DIVE WHILE YOU CLOSE

Diving in the LV while closing the clip arms to reduce the stress while closing the leaflets.
Experience from early commercial use following CE Mark*

- 24 European centers
- 150 procedures

Patient Baseline Characteristics

Etiology
- 9% FMR (%)
- 35% DMR (%)
- 56% Mixed (%)

Valve Anatomy Complexity
- 23% Pts within EII criteria
- 77% Pts beyond EII criteria

NTR/XTR Use

- % XTR
- % NTR

DMR
- 74
- 26

FMR
- 65
- 35

MIXED
- 58
- 42

Results

- MR Reduction 84% MR≤1+
- Confirmed safety for MitraClip NTR and MitraClip XTR
- Reduction in the number of grasping attempts with XTR
- Better Steering and Grasping performance of NTR/XTR vs NT
## RECOMMENDATION:

### NTR-XTR CLIP SIZE SELECTION CONSIDERATIONS

<table>
<thead>
<tr>
<th>Anatomical Considerations</th>
<th>Favored XTR</th>
<th>Favored NTR</th>
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<tbody>
<tr>
<td><strong>Leaflet insertion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longer leaflet $^1$</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>A2-P2</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Large flail $^2$</td>
<td>+</td>
<td></td>
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<tr>
<td>Redundant leaflet</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Restricted leaflet $^3$</td>
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<td>+</td>
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<tr>
<td><strong>Tissue quality</strong></td>
<td></td>
<td></td>
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<tr>
<td>Calcification of annulus and leaflet $^4$</td>
<td>+</td>
<td></td>
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<tr>
<td><strong>Gradient</strong></td>
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<tr>
<td>Smaller MV area $^5$</td>
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<tr>
<td><strong>Cordial entrapment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve commissures $^6$</td>
<td></td>
<td>+</td>
</tr>
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</table>

### Footnotes:
1. NTR clip arm length is maximum 9 mm with $\geq 6$mm of leaflet insertion needed for complete frictional element engagement.
   XTR clip arm length is maximum 12 mm with $\geq 9$ mm of leaflet insertion needed for complete frictional element engagement.
2. IFU states flail width $<15$ mm and flail gap $< 10$mm
3. IFU includes treatment of severely restricted posterior leaflet as a warning
4. IFU includes severe calcification in the grasping area and/or annulus as a warning
5. IFU states Mitral valve area $\geq 4.0 \text{ cm}^2$
6. IFU includes treatment of a primary jet outside of the A2-P2 as a warning
69 yo Female

NYHA Class III
Dyslipidemia
Paroxysmal Atrial Fibrillation

Hypertrophic Obstructive Cardiomyopathy
2013 LV Myectomy with minimal residual obstruction LVOT
Patent coronary arteries
Patient symptomatic under physical stress

Severe MR (revealed under stress test)
Normal systolic LV function
No Pulmonary hypertension
Dilated left atrium

MR in HOCM
First grasping attempt done with MitraClip NT

Several grasping attempts done but impossible to capture enough tissue from both leaflets
Second Attempt done with MitraClip \( \text{XT}^R \)

3D Clip Orientation

Mitraclip positioning below the leaflet and leaflet engagement
Leaflet Grasping and Echocardiographic evaluation

Grasping with the MitraClip XTR

No residual MR after leaflet grasping
Final Echocardiographic Result
1 month Follow Up – TTE evaluation
Mixed disease (end-stage Barlow’s, with low EF) treated with NTR

55 yo Female

NYHA Class III
Severe renal insufficiency

Marfan syndrome (proven FBN1 mutation)
2008 Repair of type A aortic dissection, EVITA, 3x CABG
Patient severely symptomatic

Severe mixed MR
Myxomatous leaflet disease
Moderate/Severe Aortic insufficiency
Maintained LVEF
No Pulmonary hypertension
Dilated left atrium
First Clip Placement
First Clip Placement
Second Clip Placement
Final Echocardiographic Result
1 month Follow Up – TTE evaluation
85 yo Female

NYHA Class III
Dyslipidemia
Permanent Atrial Fibrillation

Non-stenotic coronary atheromatosis
Patient under dialysis
Symptomatic for dyspnoea

**Severe Mitral and Tricuspid regurgitation**
Normal LVEF (80%)
Severe Pulmonary Hypertension (sPAP 55mmHg)
Dilated left and right atriums

**Tricuspid Treatment with XTr**
Result after 2 MitraClip (XTR) in mitral position

Color result after 2\textsuperscript{nd} Clip

No sign of stenosis
Tricuspid Regurgitation Focus

2D loop of Tricuspid Valve

Severe Tricuspid Regurgitation
Tricuspid Clip 3D Catheter Navigation in RA
First Tricuspid Clip Placement in ASC

1st Clip grasping in ASC

Transgastric view after 1st Clip grasping in ASC
Result after First Tricuspid Clip Placement in ASC

1st Clip release

Residual TR after 1st Clip release
Second Tricuspid Clip Placement in ASC

2nd Clip grasping in ASC

Result after grasping in ASC
Result after Second Tricuspid Clip Placement in ASC

TR before 2\textsuperscript{nd} Clip release

Bicuspid TV at 3D TEE
Final Echocardiographic Result

Final Transgastric view

3D colour at the end of the procedure
PRE Vs POST
Final Fluoroscopic Result 2XTR Mitral + 2 XTR Tricuspid
1 month Follow Up – TTE evaluation
Tricuspid Repair: TRILUMINATE Trial (CE Study)

- Prospective, single arm, multi-center trial
- At least 85 subjects will be enrolled at up to 25 sites across Europe and US
- To evaluate tricuspid valve repair system safety and performance in symptomatic patients with moderate or greater tricuspid regurgitation
- Echocardiographic TR reduction ≥1 grade at 30-days post-procedure
- A composite of major adverse events (MAE) at 6-months

LEVERAGING PROVEN Clip-BASED TECHNOLOGY for the Tricuspid valve

Tricuspid: Exclusively for clinical investigation. Currently in development at Abbott and being evaluated in clinical trials and intended for use by or under the direction of a physician. Not available for sale.
Expanding MR treatment options – Tendyne TMV Replacement

**Tendyne transcatheter mitral valve replacement (TMVR) system**
- The first and only repositionable and fully retrievable replacement valve in clinical trial
- Tri-leaflet porcine pericardial valve, apical tether, and self-expanding nitinol frame

**The most comprehensive TMVR clinical experience to-date**
- Over 150 subjects studied through ongoing global clinical trials
- Over 3 years of follow-up

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The Most Experience in TMVR: TENDYNE

<table>
<thead>
<tr>
<th>Expanded Clinical Study of Tendyne Mitral Valve System</th>
<th>SUMMIT IDE Study</th>
<th>Mitral Annular Calcification Study</th>
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</thead>
<tbody>
<tr>
<td>• Global, multicentered clinical investigation to evaluate the performance and safety of the Tendyne Mitral Valve System</td>
<td>• Prospective, randomized, controlled, multicentered clinical investigation to evaluate safety and effectiveness</td>
<td>• Prospective, single-arm, multicentered feasibility study of Tendyne for the treatment symptomatic, severe MR and severe mitral annular calcification</td>
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<tr>
<td>• 350 patients at up to 40 clinical sites across Europe and the US</td>
<td>• 1010 patients at up to 80 clinical sites</td>
<td>• 30 patients at up to 10 sites</td>
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</tbody>
</table>

Tendyne: Exclusively for clinical investigation. Currently in development at Abbott and being evaluated in clinical trials and intended for use by or under the direction of a physician. Not available for sale.