Eversense® Continuous Glucose Monitoring (CGM) System

March 29, 2018
Senseonics, Inc.
Clinical Chemistry and Clinical Toxicology Device Panel
Introduction

Mukul Jain, PhD
Chief Operating Officer
Senseonics, Inc.
Eversense Continuous Glucose Monitoring (CGM) System

90-day Implantable Sensor
subcutaneous

Removable Transmitter
worn over skin

Mobile Application
handheld device
Proposed Indication for Use

- For continually measuring glucose levels in adults (age ≥ 18) with diabetes for operating life of sensor

- System provides:
  - Real-time glucose readings
  - Glucose trend information
  - Alerts for detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia)

- Adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices
System Components: Sensor

- Inserted into upper arm
- Lasts up to 90 days
- Measures glucose every 5 min
- Silicone collar containing 1.75 mg dexamethasone acetate (DXA)
  - Reduce inflammation around sensor
Sensor Technology Based on Fluorescence
System Components: Transmitter

- Calculates glucose values and trends
- Worn externally over inserted sensor
- Secured with adhesive patch
- Vibrates for alerts and notifications
- Rechargeable
System Components: Mobile Medical Application

- Displays glucose information from transmitter
  - Values and trends
  - Alerts and notifications
- Runs on smartphone
- Reminds user to calibrate (2x/day)
- Option to upload data to Senseonics’ Data Management System
Multiple Alert Types to Ensure Safety

- **Threshold**
  - Identify glucose levels below or above pre-set values

- **Predictive**
  - Signal when alert level is expected to be crossed in immediate future (e.g. 10 minutes prior)

- **Rate of change**
  - Identify rising or falling glucose exceeding pre-set rate of change
Vibratory, Visual, and Audio Alerts

- Transmitter vibrates whether mobile app is active or in vicinity
- Unique vibration patterns
- Audible alert AND visual message on handheld device
Sensor Inserted in Upper Arm During Simple, Office-Based Procedure

- Sensor inserted/removed by HCP
- Brief, office-based procedure
- Custom insertion tools
- Procedure:
  - Skin anesthetized and disinfected
  - Small incision in upper arm
  - Blunt dissector creates subcutaneous pocket
  - Sensor transferred to pocket
  - Similar removal procedure
Eversense System Regulatory Status

- CE Mark received May 2016
- Available in 14 countries
- 1686 patients commercially
  - 2386 insertions
  - Up to 7 sequential sensors
- PMA submitted to FDA in October 2016

As of February 2, 2018
Clinical Program: 2224 Patients

- PRECISE (EU)  
  Nov 2015  
  N=81

- PRECISE II (US)  
  Jul 2016  
  N=90

- PRECISION (US)  
  Feb 2018  
  N=35

- Feasibility Studies  
  N=332

- European Patient Registry  
  Ongoing  
  N=1686  

= Ongoing study
FDA Discussion Topics: Design Changes

- Design changes since PRECISE II
  - Transmitter
  - Glucose algorithm
  - Sensor end cap
  - Blunt dissector tool
- Study results establish Eversense is safe and effective
- Changes are incremental in nature
  - Continuous improvement in design
Design Changes: Transmitter

- More ergonomic design
  - Thinner
  - Lighter
  - Less obtrusive
- Water-resistant
- Passed verification and validation testing
- Extensive EU commercial experience
Design Changes: Glucose Algorithm

- Glucose algorithm updated to improve performance in
  - Early sensor wear
  - Hypoglycemic range
- Raw sensor data independent of algorithm in transmitter
- Algorithm developed with data from EU pivotal study (PRECISE)
- Post hoc processing of US data collected with SW 602
- Eversense performance accurate and reliable with Study SW and SW 602
FDA Discussion Topics: Sensor Accuracy

- Amount of data relative to sensor life (90 days)
- Accuracy in early wear period
**PRECISE II: Eversense System is Highly Accurate**

- **Demonstrated accuracy**
  - 8.5% mean absolute relative difference (MARD)
  - 87% of readings within 15 mg/dL or 15% of reference

- **Excursions consistently detected**
  - 96% of hypoglycemic excursions*
  - 98% of hyperglycemic excursions*

- **Duration of use**
  - 91% of sensors functioned for 90 days

*Includes 70 mg/dL and 180 mg/dL thresholds and 10-minute predictive alerts
Eversense System is Safe

- No device-related SAEs
  - 1 procedure-related SAE through 90 days post-insertion
- No unanticipated AEs
- Low rate of infections and adhesive patch skin reactions
- AEs consistent with other CGMs and subcutaneous implants
Repeat Sensor Use is Safe

- Risk analysis
  - Risks are consistent, predictable, can be mitigated
  - Single insertion characterizes impact, 90-day use, removal, and healing

- Clinical study results
  - Device and insertion/removal procedure are safe
  - Nominal/complete healing following sensor removal

- Post-marketing studies of repeat use
  - EU Registry (1686 patients, up to 7 sequential sensors)
  - Repeat sensor not associated with increased AEs
## Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmet Need</td>
<td>Jeremy H. Pettus, MD University of California at San Diego</td>
</tr>
<tr>
<td>Study Design</td>
<td>Tim Goodnow, PhD Senseonics, Inc.</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Lynne Kelley, MD, FACS Senseonics, Inc.</td>
</tr>
<tr>
<td>Safety</td>
<td>Lynne Kelley, MD, FACS Senseonics, Inc.</td>
</tr>
<tr>
<td>Post-approval / Training</td>
<td></td>
</tr>
<tr>
<td>Clinical Perspective</td>
<td>Steven J. Russell, MD, PhD Harvard Medical School</td>
</tr>
</tbody>
</table>
**Additional Experts**

- **Clinical Pharmacology**
  Nicholas Fleischer, RPh PhD
  Vice President
  Clinical Pharmacology and Biopharmaceutics
  The Weinberg Group

- **Statistics**
  Richard Holcomb, PhD
  Consultant

- **Study Conduct**
  Katherine Tweden, PhD
  Senseonics, Inc.

- **Dermatology**
  Howard I. Maibach, MD
  Dermatologist
  Professor of Dermatology
  University of California, San Francisco

- **Pathology**
  Renu Virmani, MD FACC
  President
  CVPath Institute
Unmet Need

Jeremy H. Pettus, MD
Assistant Professor of Medicine
Endocrinology, Diabetes and Metabolism
University of California, San Diego (UCSD)
CGM Overview

- CGM benefits
  - Improved overall glucose control $\rightarrow$ lower HbA1c levels
  - Increased time spent within normal glucose range
  - Improved quality of life
- CGM use supported by society guidelines*
- Greatly underutilized

*American Diabetes Association, Endocrine Society, and American Association of Clinical Endocrinologists

Polonsky et al. (2017)
Intermittent Monitoring with Home Blood Glucose Meter Leads to Unnoticed Highs and Lows
Maximum A1c Improvement with Regular CGM Use

Change in A1c

<table>
<thead>
<tr>
<th>CGM Use (days/week)</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4 days</td>
<td>-0.6</td>
</tr>
<tr>
<td>4 to 6 days</td>
<td>-0.4</td>
</tr>
<tr>
<td>≥ 6 days</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

JDRF CGM Study Group (2008)
CGM Protects Against Severe Hypoglycemia

Patients with Severe Hypoglycemia per Year

- No CGM: A1c: 7.21
  - 1 event / 19 months

- CGM: A1c: 7.12
  - 1 event / 60 months

1. DCCT Research Group (1993); 2. JDRF CGM Study Group (2008)
CGM Systems Are Underutilized: 76% of Patients Do Not Use CGM

Type 1 Diabetes (T1D) Exchange registry
27% of Patients Discontinue CGM Use Within 1 Year

<table>
<thead>
<tr>
<th>Reason</th>
<th>N=262</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGM not working properly / accurate enough</td>
<td>71%</td>
</tr>
<tr>
<td>Problems with adhesive/insertion</td>
<td>61%</td>
</tr>
<tr>
<td>Too expensive / not covered by insurance</td>
<td>58%</td>
</tr>
<tr>
<td>Uncomfortable to wear</td>
<td>41%</td>
</tr>
<tr>
<td>Using pump / don’t want two sites on body</td>
<td>33%</td>
</tr>
<tr>
<td>CGM too big</td>
<td>28%</td>
</tr>
</tbody>
</table>

Type 1 Diabetes (T1D) Exchange Registry (2016)
Advancements Needed in CGM Systems

- Longer sensor life
- Less frequent sensor insertions
  - Current systems require 25–50 replacements/year
- Easy to wear and easily removed
  - For physical activities or discretion
Natural Evolution of Sensor Technology: Longer-Lasting, Less Intrusive

- Proven clinical benefit
- Many patients have not adopted CGM technology or quickly abandon it
- Patients missing opportunity to improve diabetes status and quality of life
- Need more CGM options to increase patient access
Study Design and Effectiveness

Tim Goodnow, PhD
Chief Executive Officer
Senseonics, Inc.
# Eversense Clinical Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Patients</th>
<th>Sites</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECISE II</td>
<td>90 days</td>
<td>90</td>
<td>8 US</td>
<td>Pivotal</td>
</tr>
<tr>
<td>PRECISION</td>
<td>90 days</td>
<td>35</td>
<td>3 US</td>
<td>Supportive</td>
</tr>
<tr>
<td>PRECISE</td>
<td>180 days</td>
<td>81</td>
<td>7 EU</td>
<td>Supportive</td>
</tr>
<tr>
<td>European Patient Registry</td>
<td>2 years</td>
<td>1686</td>
<td>350 EU</td>
<td>Post-market</td>
</tr>
<tr>
<td>(ongoing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feasibility Studies</td>
<td>Varied</td>
<td>332</td>
<td>10</td>
<td>Pilot</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2224</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PRECISE II: Pivotal Study Design

- Non-randomized, single-arm, multi-center study
- N=90 patients
  - n=75 one sensor inserted
  - n=15 two sensors inserted (one in each arm)
- Sensors calibrated 2x/day using home glucose meter
- Glucose readings and high/low alerts were blinded during study
## PRECISE II: Pivotal Study Schedule

<table>
<thead>
<tr>
<th>Clinic Visit</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>-30</td>
<td>0</td>
<td>1</td>
<td>30</td>
<td>60</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Screening / Follow-up</td>
<td>✔️</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Accuracy (in-clinic)</td>
<td></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Challenges*</td>
<td></td>
<td></td>
<td></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

*Meal, exercise, compression challenges

- **Insertion**
- **Removal**

**At-home wear for 90 days**
Mean absolute relative difference (MARD)
  - Compares sensor reading with reference glucose
  - Smaller MARD = higher accuracy

Percent of sensor values within 15 mg/dL or 15% of reference
Sensor accuracy across 90 days of use
Agreement of sensor readings within accuracy limits
High and low glucose alert performance
Impact of compression
Paired precision
Kaplan-Meier analysis of sensor life
Method comparison, bias analysis, Clarke & Consensus Error Analysis
PRECISE II: Key Enrollment Criteria

- Adults diagnosed with diabetes mellitus for at least 1 year
- No severe hypoglycemia within last 6 months
- No diabetic ketoacidosis requiring hospitalization within 6 months
# PRECISE II Demographics: Representative Study Sample

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 60%</td>
</tr>
<tr>
<td>Age</td>
<td>Mean 45 years</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian 86%</td>
</tr>
<tr>
<td></td>
<td>Black or African American 8%</td>
</tr>
<tr>
<td></td>
<td>Asian 3%</td>
</tr>
<tr>
<td></td>
<td>Other 3%</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>Mean 29 kg/m²</td>
</tr>
<tr>
<td>Glycosylated Hemoglobin (HbA1c)</td>
<td>Mean 7.6%</td>
</tr>
<tr>
<td>Time since diabetes diagnosis</td>
<td>Mean 20 years</td>
</tr>
<tr>
<td>Diabetes type</td>
<td>Type 1 68%</td>
</tr>
<tr>
<td></td>
<td>Type 2 32%</td>
</tr>
<tr>
<td>Type of insulin therapy</td>
<td>Continuous insulin infusion pump 48%</td>
</tr>
<tr>
<td></td>
<td>Multiple daily injections 27%</td>
</tr>
<tr>
<td></td>
<td>None (Type 2, not on insulin) 22%</td>
</tr>
<tr>
<td></td>
<td>Other (long-acting insulin only) 3%</td>
</tr>
</tbody>
</table>
**PRECISE II: Disposition**

- **Consented**
  - N=114

  - Screen failures (n=17)
  - Withdrawn prior to insertion (n=7)

- **Completed Sensor Insertion**
  - N=90

  - Lost to follow up (n=1)

- **Completed Day 1 Visit**
  - N=90

  - Withdrawn consent (n=2)
  - Sensor replacement alert (n=1)

- **Completed Day 30 Visit**
  - N=89

  - Sensor replacement alert (n=4)

- **Completed Day 60 Visit**
  - N=86

- **Completed Day 90 Visit**
  - N=82
## PRECISE II: Primary Effectiveness Endpoint Met Using Study Software

<table>
<thead>
<tr>
<th>Software Version</th>
<th>Unique Patients N</th>
<th>Paired Values N</th>
<th>Mean Absolute Relative Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study SW</td>
<td>90</td>
<td>15,704</td>
<td>8.8% (8.3%, 9.4%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Based on all evaluable data from all patients with at least one paired glucose reading between primary sensor and reference values.
## PRECISE II: Primary Effectiveness Endpoint Met Using SW 602

Based on all evaluable data from all patients with at least one paired glucose reading between primary sensor and reference values

<table>
<thead>
<tr>
<th>Software Version</th>
<th>Unique Patients N</th>
<th>Paired Values N</th>
<th>Mean Absolute Relative Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SW 602</td>
<td>90</td>
<td>15,753</td>
<td>8.5% (8.0%, 9.1%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
**PRECISE II: Sensor Accurate through 90 Days of Use**

<table>
<thead>
<tr>
<th>Study Time Point</th>
<th>Unique Patients N</th>
<th>Paired Values N</th>
<th>% of CGM Readings within 15/15% of Reference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>90</td>
<td>15,753</td>
<td>87% (84.7%, 88.6%)</td>
</tr>
<tr>
<td>Day 1</td>
<td>90</td>
<td>1708</td>
<td>77% (72.8%, 80.4%)</td>
</tr>
<tr>
<td>Day 30</td>
<td>88</td>
<td>5081</td>
<td>91% (88.3%, 92.6%)</td>
</tr>
<tr>
<td>Day 60</td>
<td>85</td>
<td>4725</td>
<td>87% (83.4%, 90.4%)</td>
</tr>
<tr>
<td>Day 90</td>
<td>77</td>
<td>4239</td>
<td>85% (81.8%, 88.4%)</td>
</tr>
</tbody>
</table>
# Eversense Clinical Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Patients</th>
<th>Sites</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECISE II</td>
<td>90 days</td>
<td>90</td>
<td>8 US</td>
<td>Pivotal</td>
</tr>
<tr>
<td>PRECISION</td>
<td>90 days</td>
<td>35</td>
<td>3 US</td>
<td>Supportive</td>
</tr>
<tr>
<td>PRECISE</td>
<td>180 days</td>
<td>81</td>
<td>7 EU</td>
<td>Supportive</td>
</tr>
<tr>
<td>European Patient Registry</td>
<td>2 years</td>
<td>1686</td>
<td>350 EU</td>
<td>Post-market</td>
</tr>
<tr>
<td>(ongoing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feasibility Studies</td>
<td>Varied</td>
<td>332</td>
<td>10</td>
<td>Pilot</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>2224</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# PRECISION Study Design

## Clinic Visit Schedule

<table>
<thead>
<tr>
<th>Clinic Visit</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>-30</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>14</td>
<td>30</td>
<td>60</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Screening/Follow-up</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy (in-clinic)</td>
<td></td>
<td></td>
<td></td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Challenges*</td>
<td></td>
<td></td>
<td></td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

- Meal challenges; Overnight challenges were performed on Days 7 and 14

![At-home wear for 90 days diagram]
PRECISION Differences from PRECISE II

- 3 US sites
- 35 patients with sensors inserted
  - 27 patients had 2 sensors inserted
- Unblinded sensor glucose values and active high/low alerts
## PRECISION:
Sensor Accurate over 90 Days of Use

<table>
<thead>
<tr>
<th>Study Time Point</th>
<th>Unique Patients N</th>
<th>Paired Values N</th>
<th>% of CGM Readings within 15/15% of Reference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>35</td>
<td>15,170</td>
<td>85% (82.9%, 87.5%)</td>
</tr>
<tr>
<td>Day 1</td>
<td>35</td>
<td>2665</td>
<td>79% (74.5%, 83.1%)</td>
</tr>
<tr>
<td>Day 7</td>
<td>35</td>
<td>2926</td>
<td>86% (81.5%, 89.7%)</td>
</tr>
<tr>
<td>Day 14</td>
<td>35</td>
<td>2997</td>
<td>88% (84.7%, 90.7%)</td>
</tr>
<tr>
<td>Day 30</td>
<td>35</td>
<td>2284</td>
<td>88% (81.3%, 92.6%)</td>
</tr>
<tr>
<td>Day 60</td>
<td>35</td>
<td>2133</td>
<td>87% (79.7%, 91.8%)</td>
</tr>
<tr>
<td>Day 90</td>
<td>35</td>
<td>2165</td>
<td>84% (78.4%, 88.2%)</td>
</tr>
</tbody>
</table>

Legend:
- Blue circle with line: % of CGM Readings within 15/15% of Reference
- Vertical line with 95% CI: Confidence Interval

Due to the nature of the data, the table and graph indicate the precision of the sensor over time, with a particular focus on the accuracy of the CGM readings compared to reference values, showing a high level of consistency and reliability throughout the 90 days of use.
# Accuracy Comparison with Approved CGMs through Sensor Life

<table>
<thead>
<tr>
<th>Device</th>
<th>Data Source</th>
<th>Percent of System Readings Within 15/15% of Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td>Eversense (SW 602)</td>
<td>PRECISE II</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>PRECISION</td>
<td>79%</td>
</tr>
<tr>
<td>Dexcom G5*</td>
<td>--</td>
<td>77%</td>
</tr>
<tr>
<td>Medtronic Guardian (3)*‡</td>
<td>--</td>
<td>68%</td>
</tr>
<tr>
<td>FreeStyle Libre*</td>
<td>--</td>
<td>76%</td>
</tr>
</tbody>
</table>

* Summary of Safety and Effectiveness Data (SSED) - Medical Device Databases - http://www.fda.gov
‡ Results based on calibration every 12 hours
# Accurate Detection of Glucose Excursions

<table>
<thead>
<tr>
<th>Alert Setting</th>
<th>PRECISE II</th>
<th></th>
<th>PRECISION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detection</td>
<td>False Alert</td>
<td>Detection</td>
<td>False Alert</td>
</tr>
<tr>
<td>Low Glucose Alert at 70 mg/dL*</td>
<td>96%</td>
<td>16%</td>
<td>95%</td>
<td>8%</td>
</tr>
<tr>
<td>High Glucose Alert at 180 mg/dL*</td>
<td>98%</td>
<td>7%</td>
<td>99%</td>
<td>7%</td>
</tr>
</tbody>
</table>

*Includes threshold and 10-minute predictive alerts
PRECISE II and PRECISION: Eversense Sensor Longevity

- PRECISE II: KM survival probability of 91% at Day 90
- PRECISION: All sensors functioned 90 days
## PRECISE II and PRECISION: System Adherence

<table>
<thead>
<tr>
<th></th>
<th>PRECISE II</th>
<th>PRECISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median wear time</td>
<td>23.4 hours</td>
<td>23.4 hours</td>
</tr>
<tr>
<td>% transmitters worn &gt; 20 hours/day</td>
<td>87%</td>
<td>91%</td>
</tr>
</tbody>
</table>
Effectiveness Summary: Eversense is Accurate for 90 Days

- PRECISE II: 87% of sensor readings with 15/15% of reference
- PRECISION: 85% of sensor readings with 15/15% of reference
- Accurate at each measured time point
- No degradation of sensor performance
  - 91% of sensors function through 90 days
  - “Sensor Replacement” alert appropriately produced
- Over 95% detection rates for glycemic excursions
  - High (180 mg/dL) and low (70 mg/dL) glucose
Clinical Safety

Lynne Kelley, MD, FACS
Chief Medical Officer
Senseonics, Inc.
Overview of Safety Profile

- Eversense system has acceptable safety profile
  - Similar to other marketed CGM systems
- Procedural risks of implantable sensor mitigated
  - Device design, training, and continued improvements based on post-market surveillance
- Eversense reduces some known risks associated with other CGM systems
# Eversense Clinical Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Patients</th>
<th>Sites</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECISE II</td>
<td>90 days</td>
<td>90</td>
<td>8 US</td>
<td>Pivotal</td>
</tr>
<tr>
<td>PRECISION</td>
<td>90 days</td>
<td>35</td>
<td>3 US</td>
<td>Supportive</td>
</tr>
<tr>
<td>PRECISE</td>
<td>180 days</td>
<td>81</td>
<td>7 EU</td>
<td>Supportive</td>
</tr>
<tr>
<td>European Patient Registry</td>
<td>2 years</td>
<td>1686</td>
<td>350 EU</td>
<td>Post-market</td>
</tr>
<tr>
<td>(ongoing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feasibility Studies</td>
<td>Varied</td>
<td>332</td>
<td>10</td>
<td>Pilot</td>
</tr>
</tbody>
</table>

**Total**: 2224
### PRECISE II and PRECISION: Device Exposure

<table>
<thead>
<tr>
<th></th>
<th>PRECISE II</th>
<th>PRECISION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensors inserted and removed</td>
<td>106 sensors (90 patients)</td>
<td>62 sensors (35 patients)</td>
</tr>
<tr>
<td>Procedures performed</td>
<td>212 procedures</td>
<td>124 procedures</td>
</tr>
<tr>
<td>Sensor use (mean duration)</td>
<td>92.2 days</td>
<td>91 days</td>
</tr>
<tr>
<td>Sensor exposure</td>
<td>9,773 days</td>
<td>6,148 days</td>
</tr>
</tbody>
</table>
PRECISE II and PRECISION: Primary Safety Endpoint

- Incidence of device-related or insertion/removal procedure-related serious adverse events (SAEs) at any point during sensor use
PRECISE II and PRECISION: Additional Safety Analyses

- Non-serious related adverse events
- AEs of special interest
  - e.g. infection, adhesive reactions
- Dexamethasone exposure over time
CO-59

PRECISE II and PRECISION: Serious Adverse Events (SAEs)

PRECISE II

- No device-related SAEs
- One procedure-related SAE reported
  - Sensor removal sensor unsuccessful (with and without ultrasound)
  - Sensor successfully removed by surgeon under general anesthesia

PRECISION

- No device- or procedure-related SAEs
  - 3 unrelated SAEs
  - Gastroenteritis, hypoglycemic episode, cellulitis of left foot
## PRECISE II and PRECISION: Device- or Insertion/Removal-Related AEs

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>PRECISE II</th>
<th>PRECISION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Patients N=90</td>
</tr>
<tr>
<td>All Events</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Bruising</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Erythema</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Device fragment not recovered</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tingling</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Delayed report of pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Secondary procedure to remove sensor</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dermatitis at patch location</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Skin hyperpigmentation</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
CO-61

All removed sensors returned to sponsor for inspection

2 devices did not have cap upon return

Corrective and preventative action plan implemented
  - Implementing enhanced quality procedures (cap adhesion)

Cap material: PMMA highly biocompatible, permanent implant
  - Orthopedic, dental, and ophthalmologic

Cap size: 3.2 mm x 0.8 mm

PRECISE II:
Two Events Related to Device Fragment
No infections

All related AEs considered expected and common for subcutaneous implant

All related AEs resolved fully
Role of Dexamethasone-Eluting Silicone Collar

- Contains 1.75 mg dexamethasone acetate (DXA)
  - Water-insoluble corticosteroid
  - Reduces local inflammatory response
  - Extends sensor life
- Controlled and slow DXA release
  - < 3 μg/day to local tissue
  - < 300 μg delivered over entire 90 days
Impact of Dexamethasone Exposure

- Blood assayed for DXA to 50 pg/mL level
  - No detectable plasma levels of DXA observed
  - No systemic effects
- DXA collars examined after removal
  - Minimal DXA exposure confirmed 3 μg/day
- 2 events of transient hyperpigmentation
  - Resolved upon sensor removal
## Eversense Clinical Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Patients</th>
<th>Sites</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECISE II</td>
<td>90 days</td>
<td>90</td>
<td>8 US</td>
<td>Pivotal</td>
</tr>
<tr>
<td>PRECISION</td>
<td>90 days</td>
<td>35</td>
<td>3 US</td>
<td>Supportive</td>
</tr>
<tr>
<td>PRECISE</td>
<td>180 days</td>
<td>81</td>
<td>7 EU</td>
<td>Supportive</td>
</tr>
<tr>
<td>European Patient Registry</td>
<td>2 years</td>
<td>1686</td>
<td>350 EU</td>
<td>Post-market</td>
</tr>
<tr>
<td>(ongoing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feasibility Studies</td>
<td>Varied</td>
<td>332</td>
<td>10</td>
<td>Pilot</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>2224</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Integrated Device Exposure

- Three multi-center studies
  - PRECISE II, PRECISION, and PRECISE
- 206 subjects
- 335 sensors
- 670 insertion/removal procedures
- 22,529 patient-days of sensor wear
# Integrated Summary of Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Events</th>
<th>Patients N=206</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Events</td>
<td>41</td>
<td>26 (13%)</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>10</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Redness/erythema</td>
<td>6</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Secondary procedure to remove sensor</td>
<td>4</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Bruising/hematoma</td>
<td>3</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Device fragment not recovered</td>
<td>2</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Dermatitis at patch location</td>
<td>3</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Skin hyperpigmentation</td>
<td>2</td>
<td>1 (&lt; 1%)</td>
</tr>
</tbody>
</table>

Events occurring once: neuropathy, vertigo, disturbed sleep, headache, paresthesia, syncope, hypertension, and nausea
Low Rate of Infections Observed in Studies

- Aggregate infection rate 1%
- Improved incision care instructions
  - PRECISE: leave bandage for 24 hours
  - PRECISE II: leave bandage for 48 hours
- Infection rate observed is below literature reports for similar implants and minor procedures: 2–4%*

*Buprenorphine, Braeburn Pharmaceuticals, Inc.
## Eversense Clinical Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Patients</th>
<th>Sites</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRECISE II</td>
<td>90 days</td>
<td>90</td>
<td>8 US</td>
<td>Pivotal</td>
</tr>
<tr>
<td>PRECISION</td>
<td>90 days</td>
<td>35</td>
<td>3 US</td>
<td>Supportive</td>
</tr>
<tr>
<td>PRECISE</td>
<td>180 days</td>
<td>81</td>
<td>7 EU</td>
<td>Supportive</td>
</tr>
<tr>
<td>European Patient Registry</td>
<td>2 years</td>
<td>1686</td>
<td>350 EU</td>
<td>Post-market</td>
</tr>
<tr>
<td>(ongoing)</td>
<td>Varied</td>
<td>332</td>
<td>10</td>
<td>Pilot</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2224</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
European Patient Registry

- All patients inserted commercially enrolled in registry
  - Enrollment completed when 100 patients reach 4 insertions
- All patients enrolled to be followed through 8 insertions and removals
## Low Rate of AEs with Repeat Insertions

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Post Insertion #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 N=1686</td>
</tr>
<tr>
<td>SAEs</td>
<td>0</td>
</tr>
<tr>
<td>Device-, procedure-related AEs</td>
<td></td>
</tr>
<tr>
<td>Infection (at sensor site)</td>
<td>8 (0.5%)</td>
</tr>
<tr>
<td>Secondary procedure to remove sensor</td>
<td>7</td>
</tr>
<tr>
<td>Adhesive patch site irritation</td>
<td>5</td>
</tr>
<tr>
<td>Prolonged wound healing</td>
<td>3</td>
</tr>
<tr>
<td>Redness/reaction to dressing</td>
<td>3</td>
</tr>
<tr>
<td>Sensor broke during removal</td>
<td>3</td>
</tr>
<tr>
<td>Skin atrophy over sensor w/ skin discoloration</td>
<td>2</td>
</tr>
<tr>
<td>Skin atrophy over sensor</td>
<td>1</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>1</td>
</tr>
<tr>
<td>Sensor site pain/discomfort</td>
<td>1</td>
</tr>
<tr>
<td>Bruising</td>
<td>1</td>
</tr>
<tr>
<td>Patient fainted during procedure</td>
<td>1</td>
</tr>
<tr>
<td>Hematoma</td>
<td>-</td>
</tr>
</tbody>
</table>
Proposed Post-Approval Study
Proposed U.S. Post Approval Study Design

- Serial sensor insertions and removals for 2 years
- 175 patients in up to 20 clinical sites

**Primary safety endpoint**
- Rate of device-related and insertion/removal procedure-related SAEs through 12 months ≤ 7%

**Primary effectiveness endpoint**
- Time in range (between 70 mg/dL and 180 mg/dL), 12 months vs. first month
Proposed U.S. Post Approval Study: Other Outcome Measures

- All related AEs through 2 years
- Plasma dexamethasone levels every 6 months
- Effectiveness of training program
  - Success rate of insertions/removals
- Diabetes distress scale and CGM satisfaction scale
  - Baseline and annually
Design Changes

- Sensor end cap
- Blunt dissector tool
Sensor End Cap Improvement

- End cap redesigned to be flush with end of sensor
- Design verification
  - Compressive forces
  - Torque
  - Maintains functional compatibility with insertion tool
Blunt Dissector Design Improvement

- Same function
- Consistent placement facilitates removal
  - Proper entry angle
  - Pocket depth / length
  - Parallel to skin
- Validated with Human Factors testing
Training for Clinicians
Training Program Overview

- Mandatory comprehensive training
- Certification process led by Senseonics approved trainers
  - Didactic session
  - Practices with simulated skin
  - Initial insertions and removals are observed

Training resources:
- CGM Sensor Insertion and Removal Instructions
- Insertion videos
- Removal videos
- Simulation station
- Procedure poster
- Take-home instructions
Training Checklist for Certification

Pre-Work before Simulation Training

- Learning curve: ~2 to 3 procedures
- 3 patients scheduled in same day to familiarize with procedure

Pre-Work before Removal Review

- Learning curve: ~2 to 3 procedures
- 3 patients scheduled in same day to familiarize with procedure
Hands-On Practice Session with Simulated Skin, Sterile Field, and Required Supplies
Examples of Training Materials

Insertion of the Eversense CGM Sensor
This video provides step-by-step instructions to the Eversense Insertion Procedure process. The content is designed for a healthcare provider or training. Topics include patient selection, sensor site considerations, sensor placement technique, and patient care instructions.

Advanced Sensor Removal Guidance
Eversense Sensor Removal Procedure and Potential Complications in the Eversense CGM Sensor Insertion and Removal Instructions:
- A topical sensor removal takes between 5 and 10 minutes.
- The correct type of clamp must be available before attempting a removal. The Eversense clamp is the preferred tool. Clamps that are too small can cause scratching the sensor difficulty.
- Removal done by any provider should be done under local anesthesia, in an exam or procedure room. There is no need for the infection of normal anesthetic area in the umbilical or umbilical incision.
- Prior to starting the area, use the frictional and placement guide to get the foot signal conductive. Help the author of the technique. This will facilitate the area of where the sensor is, which will keep the umbilical crease from the hair or adel.
- If you can palpate the sensor mark both ends or cut out it by using a marker for reference.
Trained Providers Outside U.S.

- 461 clinicians trained on insertions
  - 94% certified to do insertions independently
- 258 clinicians trained on removals
  - 86% certified to do removals independently
Europe: Successful Insertion and Removal Training

- Procedure easily learned by physicians with no prior Eversense experience
- 99% of removals successful on first attempt
- Low infection rate (0.5%)
100% of insertions and 99% of removals successful on first attempt
91% of insertions and 80% of removals completed in < 5 min

<table>
<thead>
<tr>
<th></th>
<th>Insertion</th>
<th>Removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>168</td>
<td>168</td>
</tr>
<tr>
<td>Mean time</td>
<td>2.3 min</td>
<td>4.5 min</td>
</tr>
</tbody>
</table>
Eversense System Has Acceptable Safety Profile

- No unanticipated adverse events
- Limited AEs related to device or procedure
  - All AEs reported resolved fully
  - No Infections in US clinical trials
  - No detectable blood levels of dexamethasone
- One procedure-related SAE, resolved
- No device-related SAEs
- Eversense is safe for intended use
Clinical Perspective / Benefit-Risk

Steven J Russell, MD, PhD
Associate Professor of Medicine
Harvard Medical School
Relevant CGM Experience

- Experience with all currently approved CGMs (since 2004)
  - Published accuracy comparison studies of CGMs
- Developing bionic pancreas
  - Depends on CGM accuracy and reliability
  - Motivates interest in new CGM technologies
- Clinical investigator in artificial pancreas trials
  - Used Eversense system
  - Inserted and removed sensors
  - Trained quickly
Current Situation:
Majority of Patients Do Not Meet Glycemic Goals

- 70% not at A1c targets*
  - Hypoglycemia still very common
- CGM systems are proven to help
  - Improve glucose control
  - Lower risk of hypoglycemia
  - Improve patients’ lives

*Type 1 Diabetes Exchange
The Current Situation:
Only 3 Out of 10 Patients with T1D Use CGM

- Perceived burden of repeat insertion
- Fear of pain
The Current Situation:
1 out of 3 CGM Users Discontinue within 1 Year

- Problems with adhesive / insertion
- Uncomfortable
Eversense Addresses Many Barriers to CGM Use

- Longer sensor life (90 days)
- Less frequent sensor insertions
  - Eversense: 4 times per year
  - Current systems: 25–50 times per year
- Easy to wear and easily removed
  - For physical activities or discretion
- On-body vibration from transmitter provides extra safety measure
The Goal: Increase Use of CGM

- Improve glucose control
- Lower risk of hypoglycemia
Eversense® Continuous Glucose Monitoring (CGM) System

March 29, 2018
Senseonics, Inc.
Clinical Chemistry and Clinical Toxicology Device Panel