Soluble protein AXL as a Heart Failure biomarker
Content

1. The Institutions

2. The Product
   a) Target Indications
   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
   e) IPR protection
   f) Pitfalls & Risks to be considered

3. Partnering Opportunities
1. The Institutions

Group of highly specialized cardiologists in Heart Failure and Heart Transplantation from the Cardiology Department at Hospital Clinic of Barcelona

Basic researcher Montserrat Batlle, Ph.D. in Biomedical Sciences: 1995-2001, Mount Sinai Hospital-NYU, New York

The Product

a) Target Indications

Heart failure (HF) is a syndrome characterized by the following features:
- Shortness of breath at rest or during exertion, and/or fatigue
- Fluid retention such as pulmonary congestion or ankle swelling
- Objective evidence of an abnormality of the structure or function of the heart at rest

Causes: HF can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. HF constitutes the end-stage of many cardiopathies.

The invention relates to a new method for the prognosis and diagnosis of Heart Failure (HF) based on the determination of soluble AxL protein in serum.
The Product

a) Target Indications

- **HF Prevalence**: Prevalence is about 2-3% but in 70-80 year old people is between 10-20%\(^{(1)}\)

Projected changes based on the population aging in USA \(^{(2)}\)

### Prevalence

<table>
<thead>
<tr>
<th>Year</th>
<th>HF Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>2.8%</td>
</tr>
<tr>
<td>2030</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

### Direct medical costs

<table>
<thead>
<tr>
<th>Year</th>
<th>Billions of $</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>24.7</td>
</tr>
<tr>
<td>2030</td>
<td>77.7</td>
</tr>
</tbody>
</table>

### Indirect medical costs

<table>
<thead>
<tr>
<th>Year</th>
<th>Billions of $</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>9.7</td>
</tr>
<tr>
<td>2013</td>
<td>17.4</td>
</tr>
</tbody>
</table>

\(^{(1)}\) Eur J Heart Fail 2012 Aug;14(8):803-869
\(^{(2)}\) Circulation 2011 Mar 1;123(8):933-944
The Product

a) Target Indications

Data about HF hospitalizations at the HCB, year 2012

Total number of hospitalizations due to HF 425

Total days of hospitalizations due to HF 3,692
mean=8.5 days
between 1-48 days

3.692 days= 10.3% total capacity Cardiology Department
3.692 days= 1.5% total capacity HCB

Total Cost of hospitalizations 1,203,929€
Mean cost/hospitalization 2,833€
The Product

a) Target Indications

Management of Chronic Heart Failure in Adults: Synopsis of the National Institute for Health and Clinical Excellence Guideline.

Risk stratification
Specialist assessment needed
Disease progression

The Product

a) Target Indications

Management of Chronic Heart Failure

HF patient

Risk stratification

Good-prognosis patient
Follow-up at primary care
Optimization of health costs

Bad-prognosis patient
Follow-up at tertiary care
Reduction of HF Hospitalizations

Direct medical costs

2010: 24.7 billions of $
2030: 77.7 billions of $

Billions of $
The Product

b) Innovative mechanisms of action

Gas6 is the ligand

Protein S

Gas6 Receptors

MerTK

Tyro3

Axl
The Product

b) Innovative mechanisms of action

AXL roles related to cardiovascular diseases?

A) role in the vascular response to different injuries:


B) GAS6 facilitates the interactions between endothelial cells, platelets, and leukocytes *Blood.* 2008;111:4096, *Circ Res.* 2006; 98: 1446
### The Product

c) Differential features facing the market

<table>
<thead>
<tr>
<th>Feature</th>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) sAXL is very stable in serum</td>
<td>Lower manipulation cost and easier technology</td>
</tr>
<tr>
<td>B) sAXL levels in controls do not correlate with age</td>
<td>No need of different cut-offs</td>
</tr>
<tr>
<td>C) Patients from Chronic Obstructive Pulmonary Disease (COPD) do not have high sAXL levels</td>
<td>Discrimination between dyspnea due to HF or COPD</td>
</tr>
<tr>
<td>D) There is no increase of sALX in patients with Atrial Fibrillation or post-Acute Myocardial Infarction</td>
<td>Discrimination between HF and other Cardiovascular Diseases</td>
</tr>
</tbody>
</table>
The Product

c) Differential features facing the market

D) Measures of the HF biomarkers BNP and NT-proBNP have a high cost

E1) sAXL serum levels DO NOT correlate with echocardiographic parameters: LVESD, LVEDD, LVEF, LAD, IVST, LVPWT

E2) Linear regression analysis indicates that serum BNP levels were not predictive of sAXL levels

≥ Cost of sAXL measure

sAXL levels are not dependant on myocyte stretch

Different behavior from BNP and NT-proBNP
The Product

d) Current status of development

Patient enrolment

Controls (n=67)

Chronic HF patients (n=192)
NYHA II, III or IV
Reduced Ejection Fraction

Clinical data /ECG
Echocardiography
Laboratory values
Serum/plasma samples
6MWT

Patient 1 year follow-up

stable

phone call follow-up
Events = no

Non-stable

phone call follow-up
Events = yes

EVENTS
Heart Transplantation
Mortality
HF hospitalizations

HF biomarker
AXL protein is higher in myocardial samples from end-stage HF patients than in controls
The Product

d) Current status of development

Soluble AXL protein is higher in serum samples from HF patients than in controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls (C)</th>
<th>Heart Failure (HF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>67</td>
<td>192</td>
</tr>
<tr>
<td>sAXL ng/mL</td>
<td>67.8±2.0</td>
<td>86.3±2.0</td>
</tr>
</tbody>
</table>

****P<0.0001
The Product

d) Current status of development

**Discrimination**

ROC curve
AUC=0.72
[95% IC = 0.649-0.782]

**Soluble AXL protein levels discriminate between HF patients and controls**

****P<0.0001
The Product

d) Current status of development

Differences in Functional Class

<table>
<thead>
<tr>
<th>Group</th>
<th>HF class II</th>
<th>HF class III-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>138</td>
<td>54</td>
</tr>
<tr>
<td>sAXL ng/mL</td>
<td>80.9±2</td>
<td>100.2±5.0</td>
</tr>
</tbody>
</table>

Soluble AXL protein is higher in serum samples from HF patients in NYHA functional class III-IV than HF patients in class II.

****P<0.0001
The Product

d) Current status of development

- Increase in HF patients with Preserved Ejection Fraction (HF-PEF) serum

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls (C)</th>
<th>Heart Failure (HF-PEF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>67</td>
<td>25</td>
</tr>
<tr>
<td>sAXL ng/mL</td>
<td>67.8 ± 2.0</td>
<td>85.4 ± 7.3</td>
</tr>
</tbody>
</table>

Soluble AXL protein is higher in serum samples from HF patients with preserved ejection fraction than in controls

*P<0.05
The Product

d) Current status of development

sAXL serum levels directly correlated with:
- BNP levels
- serum creatinine levels
- C reactive protein
- uric acid

sAXL serum levels inversely correlated with:
- systolic blood pressure
- diastolic blood pressure
- 6-minutes walk distance
- glomerular filtration rate
- hemoglobin
- hematocrit
- hematies count

Correlation of sAXL levels with other parameters

Worse HF prognosis
The Product

d) Current status of development

- **cut-off point = sAXL 3rd quartile**
  - L-sAXL < 98.1 ng/mL
  - H-sAXL > 98.1 ng/mL

- **1 year follow-up**

**HF events:**
- Heart transplantation
- All-cause mortality
- HF-hospitalizations

- **sAXL levels in serum are predictive of HF events at short-term follow-up**
  - *** P<0.001
  - Hazard ratio = 3.3
Programa Cooperación Farma-Biotech
X encuentro (27 de noviembre de 2013)

The Product

d) Current status of development

1 year follow-up

cut-off point = BNP 3rd quartile

H-BNP > 362.7 pg/mL

HF events:
Heart transplantation
All-cause mortality
HF-hospitalizations

**** P<0.0001
Hazard ratio = 4.4

BNP levels in serum are predictive of HF events at short-term follow-up

L-BNP < 362.7 pg/mL

Percent non-HF event

Days

0
150
300
450

0
20
40
60
80
100

0
20
40
60
80
100
**Programa Cooperación Farma-Biotech**  
**X encuentro (27 de noviembre de 2013)**

**The Product**

d) Current status of development

<table>
<thead>
<tr>
<th>Percent non-HF event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

- **L-sAXL and/or L-BNP**
- **H-sAXL >98.1 ng/mL**
- **H-BNP >362.7 pg/mL**
- **H-sAXL >98.1 ng/mL + H-BNP >362.7 pg/mL**

**1 year follow-up**

cut-off point = sAXL + BNP 3rd quartile

- **L_sAXL and/or L_BNP vs H_sAXL and H_BNP**
- **** P<0.0001
- Hazard ratio = 6.8

**Use of sAXL adds predictive value to BNP**
The Product

a) Target Indications

**Management of Chronic Heart Failure**

- **HF patient**
  - **Risk stratification**
    - **sAXL**
      - **N=425**
  - **Follow-up at primary care**
    - **Optimization of health costs**
      - **(HF Cost 1.203,929€ at HCB, 2012)**
  - **Good-prognosis patient**
  - **Bad-prognosis patient**
    - **Follow-up at tertiary care**
      - **Reduction of HF Hospitalizations**
The Product

c) Differential features facing the market

2013 ACCF/AHA Guidelines for the Management of Heart Failure

Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.

Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF, besides BNP or NT-proBNP.
The Product

e) IPR protection

A European patent application filed on **February 2012**: EP12382048

PCT application filed on **August 2013**: PCT/EP2013/052743

• INVENTORS: Dra. Montserrat Batlle and Dr. Pablo García de Frutos
• APPLICANTS: IDIBAPS and CSIC
• TITLE: *Use of the soluble form of AXL in the diagnosis and/or prognosis of Heart Failure Syndrome*

The Extended European Search Report (EESR) considered that the patent complied with the conditions of novelty and industrial application

## The Product

### f) Pitfalls & Risks to be considered

- The natriuretic peptides (BNP, NT-proBNP) are well established in the HF field

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Study Population</th>
<th>NYHA FC</th>
<th>n</th>
<th>Events</th>
<th>Years follow-up</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>sAXL</td>
<td>Chronic HF</td>
<td>II-IV</td>
<td>192</td>
<td>M, HT, HF-hosp</td>
<td>1</td>
<td>Predictor of major HF events</td>
<td></td>
</tr>
<tr>
<td>Troponina-I</td>
<td>Advanced, Chronic HF</td>
<td>III-IV</td>
<td>238</td>
<td>M, urgent HT</td>
<td>1.5</td>
<td>Predictor of mortality + urgent HT</td>
<td>Circ 2003;108:833</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>Chronic HF</td>
<td>I-IV</td>
<td>133</td>
<td>M, HT, HF-hosp</td>
<td>5</td>
<td>Predictor of mortality</td>
<td>Am J Cardiol 2011;108:385-390</td>
</tr>
</tbody>
</table>

M all-cause mortality, HT heart transplantation, HF-hosp heart failure hospitalizations
Partnering Opportunities

We are looking for companies interested to further develop this technology via:

- Collaboration (Option Agreement)
- Licensing out the patent (License Agreement)

FURTHER DEVELOPMENT and VALIDATION:

- Further analyze sAXL levels in a broader HF cohort and with a longer follow-up period
- Further analyze sAXL as a biomarker for HF patients with preserved ejection fraction
- Further analyze sAXL application to discriminate HF from other pathologies
- Improvement of ELISA assay: obtaining new Antibodies based on our own recombinant material and using state of the art techniques for sAXL quantification in serum
Programa Cooperación Farma-Biotech
X encuentro (27 de noviembre de 2013)

Contact Information: mbatlle@clinic.ub.es
pablo.garcia@iibb.csic.es