PharmaMar’s Clinical Pipeline:
Summary of Licensing Opportunities

May, 2012
PharmaMar and the Zeltia Group

**Biotech companies:**
- Founded in 1939
- Pharmaceutical and chemical leader in Spain for over 60 years
- Quoted in Spanish Stock Exchange (ZEL)

**Chemical companies:**
- Founded in 1986
- Wholly owned by Zeltia Group
- 300 employees
- Headquarters in Madrid (Spain)
- Office in New York (USA)
- GMP Drug Production facilities in headquarters

“To Advance Cancer Care Through the Discovery and Development of New Marine-Derived Drugs”
PharmaMar’s Business Model

- **Marine Expeditions**
  - Biodiversity: a library of unique molecules from marine sources

- **Preclinical Testing**
  - New chemical scaffolds & New MoAs

- **Medicinal Chemistry**
  - Synthesis of identified NCEs
  - Activity optimization

- **Clinical Trials**
  - International clinical development in all countries

- **Production GMP facilities**
  - Keeping last steps of purification or synthesis within PharmaMar

- **IP and Trademarks**
  - Broad patent coverage

- **Marketing & Sales**
  - Commercial organization in EU
  - License US & RoW
Unique Strategy

- Our team of divers collects marine samples all over the world [about 10 expeditions/year]. Pharma Mar’s unique library consists of 200’000 extracts derived from ~110’000 samples from marine organisms. This library is available for licensing for screening for any pharmaceutical purpose.

- Samples are processed at our headquarters and active principles, as determined by in vitro cell assays, are purified and characterized by the most modern chemical analytical methods.

- Only compounds free of patent interference and amenable to synthesis in laboratory are selected.

- A third requirement is that the mechanism of action of the compound be distinct from other compounds, as determined by the compare analysis [NCI and Oncotest].

- Work in our own laboratories to optimize compound properties and establish synthesis routes amenable to industrial scale up.

- Continue preclinical mechanism of action and biomarker studies during clinical development of the compound.
### PharmaMar – Clinical Pipeline

<table>
<thead>
<tr>
<th>Phase</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre registration</strong></td>
<td>EU, RoW</td>
<td>EU, RoW</td>
<td></td>
</tr>
</tbody>
</table>

**Yondelis® trabectedin**

*Ecteinascidia turbinata*  
>12,000 patients treated

- Soft Tissue Sarcoma (STS) – 2nd/3rd line  
- Ovarian Cancer – 2nd line (Yondelis® + Doxil®)
- STS related to translocations – 1st line
- STS doxorubicin combo – 1st line

**Aplidin® plitidepsin**

*Aplidium albicans*  
>800 patients treated

- Multiple Myeloma dexamethasone combo  
- ODS granted

**Zalypsis® PM00104**  
>200 patients treated

- Multiple Myeloma

**Lurbinectedin**

*Synthesis*  
>140 patients treated

- plat.-res. Ovarian Cancer  
- Pancreatic Cancer monotherapy 2nd line  
- Breast Cancer  
- Acute Leukemia  
- Solid Tumors gemcitabine & doxorubicin combo

**PM060184**  
>35 patients treated

- Solid Tumors
Mechanisms of Action

- **Yondelis®**: First generation DNA minor groove binder recognizing the AGC triplet and crosslinking to arginine 961 of the nucleotide excision repair protein XPG, association with translocations present in certain soft-tissue sarcomas

- **Aplidin®**: A Rac1 activator, binding to a high-affinity membrane receptor. Triggers sustained activation of Rac1 and JNK, increases level of ROS and decreases levels of GSH. Induction of oxidative stress resulting in caspase activation and apoptotic cell death

- **Zalypsis®**: Potent DNA minor groove binder. Acts by interaction with transcriptional processes, stimulates polyADPribose polymerase

- **Lurbinectedin (PM01183)**: Novel DNA minor groove binder, preferentially recognizing the CGG triplet

- **PM060184**: Novel tubulin polymerization inhibitor