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Company Highlights

- **A clinical stage** biopharmaceutical company developing innovative therapies in the field of **Epigenetics**
- **Two molecules** already with **positive data in humans**
- Large IP portfolio with technology fully developed in-house
- MADX: ORY  A **publicly traded** company on the **Spanish Stock Exchange**
- Integrated in the **IBEX Small Cap Index**

- Raised an aggregate of circa **€85M** (in 2015-2019)
- Cash runway expected till **2H2021**
- One of the most **LIQUID** companies in the MicroCap group in the Spanish Stock Market
  - 45.7 M Shares outstanding. Fully diluted
  - 350,000 daily volume (Avg Traded Volume in 2018)
  - +88M shares negotiated in 2018 / ≈5 months for share full turnover

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* On July 26th, the company completed a Private Placement with International Investors raising gross proceeds of €20M (circa $22.2M at the exchange rate on that day)
Epigenetic dysfunctions are associated with aberrant gene expression and disease.

Epigenetic drugs can restore these transcriptional imbalances.

Lysine specific histone demethylase 1 (LSD1), aka KDM1A, removes methyl marks at mono- and dimethyl-H3K4 (histone H3 lysine 4) and H3K9 (histone H3 lysine 9).

LSD1 is the most abundant histone demethylase in the prefrontal cortex.
Oryzon is pioneering epigenetics in CNS and active in oncology

A broad pipeline to address unmeet medical needs with an attractive market opportunity

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>STUDY*</th>
<th>RESEARCH</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE IIA</th>
<th>PHASE IIB</th>
<th>PHASE III</th>
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<tbody>
<tr>
<td>VAFIDEMSTAT (ORY-2001) - dual LSD1-MAO B inhibitor</td>
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<tr>
<td>Aggression in BPD</td>
<td>REIMAGINE / PORTICO (*)</td>
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<td>Aggression in ADHD</td>
<td>REIMAGINE / ENTRANCE (*)</td>
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<td>Aggression in ASD</td>
<td>REIMAGINE / COLONNADE (*)</td>
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<tr>
<td>Aggression in AD</td>
<td>REIMAGINE-AD / GATEWAY (**)</td>
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<td>Alzheimer's disease (Mild Moderate)</td>
<td>ETHERAL monotherapy</td>
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<td>Multiple Sclerosis (RR &amp; SP)</td>
<td>SATEEN monotherapy</td>
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<td>IADADEMSTAT (ORY-1001) - selective LSD1 inhibitor</td>
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<td>AML (Elderly Unfit)</td>
<td>ALICE Combo w Aza</td>
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<td>SCLC (First Line Relapsed)</td>
<td>CLEPSIDRA Combo w Platinum/Etoposide</td>
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<tr>
<td>ORY-3001 - selective LSD1 inhibitor</td>
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<td>Non Oncological</td>
<td>Preclinical finished</td>
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<td>OTHER PROGRAMS</td>
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** CNS Market Need **
- 45 million people with AD worldwide; 20% shows aggressiveness
- Aggression is a common feature in many psychiatric diseases. +50% in ADHD(***)
- Global BPD market expected to grow to $2.6B in 2027
- AD main disruptions: memory loss, aggression and apathy. AD global costs per annum of $605B

** Oncology Market Need **
- Global AML market of $990m in 2019. Room for new Combos according to KoLs
- SCLC is a serious unmet medical need, with a MOS of 8–12 months and 5% 2-year OSR
- Global SCLC market +300,000 patients/y. FDA approved label extension of Pembro but only 19% of ORR (****)
- Projections of Rova-T when in Phase III were +5B peak sales/y

(* ) IN BLUE, NEW PHASE III STUDIES UNDER PREPARATION OR EVALUATION
(****) Contingent to + results in REIMAGINE-AD
(****) Keynote study in 83 patients
VAFIDEMSTAT a Phase II Clinical Stage Compound with a broad developability in CNS diseases

- Vafidemstat is a small molecule that selectively inhibits LSD1 and MAO-B
- LSD1 inhibition is the major driver of the pharmacological action
- Excellent Pharmacology. High oral bioavailability
- Positive results in 7 different animal models and in in-vitro models
  - Cognition
  - Neuroprotection
  - Neuroinflammation
  - Social Withdrawal / Apathy
  - Aggression / Agitation
  - Others
- Epigenetic MoA that modulates neuroinflammation and expression of key plasticity neuronal genes
- Biomarkers identified
- Good Safety in humans in Phase I+II trials with +220 participants so far
- BBB penetrance and (indirect) human brain target engagement established
- Pharmacologically active in humans

In Phase IIa in multiple clinical studies
Phase IIb studies under preparation
Vafidemstat, and LSD1 inhibition, improves cognition

In Alzheimer’s SAMP8 model vafidemstat restores memory by the NORT model.

In Huntington disease R6/1 model vafidemstat improves memory by the NORT model.

In Schizophrenia SETD1a +/- model iadademstat (ORY-1001) improves working memory.

In Psychosis & Schizophrenia NMDA receptor-hypofunction mice model T-448 (TAKEDA) LSD1 inhibitor improves memory.

Vafidemstat Fully Restores Memory Measured by NORT in SAMP8 AD Model

MILD
Treated from month 5 during 1 week
Treated from month 6 during 1 month (Delayed start-1)

MODERATE
Treated from month 5 during 1 month, tested at month 7 (1 month after treatment cessation)

SEVERE
Treated from month 8 during 4 months (Delayed start-2)

Cognition and memory impairments are found in AD and dementias but also in Autism, Schizophrenia, Depression, Bipolar disorder and other psychiatric conditions.
Vafidemstat Produces Significant Behavioural Changes

Vafidemstat Reduces Aggression in the Resident Intruder Test in the SAMP8 AD Mice model

Vafidemstat Enhances Sociability in the Three-Chamber Test in SAMP8 AD Mice

Vafidemstat Reduces Social Withdrawal in the Rat Isolation Model

**TCT - Females 12M age**
4 months treatment
Chamber Preference

- **Object Chamber**
- **Mice Chamber**

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>SAMR1 - VEH</th>
<th>SAMP8 - VEH</th>
<th>SAMP8 ORY-2001 (0.96 mg/kg/day)</th>
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<tbody>
<tr>
<td>0</td>
<td>300</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>100</td>
<td>200</td>
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<tr>
<td>400</td>
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</table>

**Number of evitations**

<table>
<thead>
<tr>
<th>Control</th>
<th>Isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veh</td>
<td>Veh</td>
</tr>
<tr>
<td>0.16</td>
<td>0.48</td>
</tr>
</tbody>
</table>

**ORY-2001 (mg/kg/day)**

- **Veh**
- **Veh**
- **0.16**
- **0.48**

*** *** *
MoA: an upstream epigenetic mechanism producing a dual activity, anti-inflammatory and prosynaptic

LSD1 localizes *in vivo* to enhancers and promoters of confirmed CNS disease risk genes
LSD1 binds to TFs that control IEG expression and stress in the PFC-amygdala axis, including SRF

- **vafidemstat up-regulates** genes associated with:
  - **Cognition**, notably memory and **executive functioning**
  - **Neuroplasticity**

- **vafidemstat potentiates** the response capacity of IEGs to stress
- **vafidemstat reduces** the expression of **inflammatory** genes including S100A9 and others

---

LSD1 inhibition rescues the axon branching deficits in the Setd1a +/- mice

Vafidemstat potently **down-regulated** the expression of a subset of genes related to immune reaction and **inflammation as S100A9** involved in OPC defective remyelination

- **Baiap3**: involved in retrograde trafficking
- **Prph**: mutated in Amyotrophic Lateral Sclerosis (ALS),
- **Fabp7**: upregulation in drosophila favors long term memory consolidation
- **Doc2a**: activity-dependent modulator of excitatory synaptic transmission, relevant to memory formation
- **Kremen2 and Rspo1**, regulators of the WNT pathway

---

In *invitro* axon branching rescue assays ORY-1001 was 1000-fold more potent than TCP

Mukai et al 2019 [httpdx.doi.org/10.1101/529701](httpdx.doi.org/10.1101/529701)

Recapitulation and reversal of schizophrenia-related phenotypes in Setd1a-deficient mice
Vafidemstat: Safety demonstrated in a Phase I study

Safe and well tolerated in a +100 healthy volunteers (young and elderly) Phase I (MAD+SAD) study

- No hematological impact at planned doses
- Efficiently crossed the BBB (70-90%)
- Oral PK - Half Life of 22h allowing once daily oral
- PK/PD data allowed definition of recommended Phase II doses

Safe and well tolerated so far in diverse Phase II studies

- Vafidemstat has been already administered to +220 volunteers and patients
- Phase IIs (MS, AD, ADHD, BPD and ASD patients) with no safety signals to date
- Longest exposure to date: 15 months
**Vafidemstat: REIMAGINE - a Basket trial in aggression**

<table>
<thead>
<tr>
<th>Duration</th>
<th>8 Weeks treatment + 4 weeks of follow up</th>
</tr>
</thead>
</table>

**Cohorts to be recruited**

**REIMAGINE:**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline Personality Disorder</td>
<td>6 patients</td>
<td>Done – Data reported in April 2019</td>
</tr>
<tr>
<td>Attention Deficit and Hyperactivity Disorder</td>
<td>6 patients</td>
<td>Done – Data reported in April 2019</td>
</tr>
<tr>
<td>Autism Spectrum Disorder</td>
<td>6 patients</td>
<td>Done – Data reported in Sept 2019</td>
</tr>
</tbody>
</table>

**REIMAGINE-AD:**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>12 patients</td>
<td>Recruitment Finished (1st report expected in Dec 2019)</td>
</tr>
</tbody>
</table>

**Endpoints**

Safety

Efficacy:

- Aggression / Agitation measured by CGI-S
- Aggression / Agitation measured by CGI-I
- Aggression / Agitation measured by NPI A/A 4 items
- Psychiatric status measured by NPI Global assessment (12 items)
- Change in specific disease scales
REIMAGINE the first proof of concept for vafidemstat in human patients

Patients of the three psychiatric indications: Borderline Personality Disorder (BPD) Attention Deficit and Hyperactivity Disorder (ADHD) and Autistic Spectrum Disorder (ASD) Treated With Vafidemstat Showed a Reduced Aggressivity

Secondary Endpoints: Efficacy

Significant improvements in aggression evaluated using the Neuropsychiatric Inventory 4-item agitation/aggression score (NPI-A/A)

Also significant improvements in aggression evaluated using the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales

Data presented at

[Event Logos]
The significant improvements in the NPI global score and overall specific scales for BPD and ADHD suggest that vafidemstat has a broader psychiatric effect beyond aggression.
Next steps: Vafidemstat, a meaningful therapeutic option for BPD

"I find myself able now to control my negative emotions and my frustration"

Patient with severe borderline personality disorder during treatment with vafidemstat. Testimony to her psychiatrist Dr. Marc Ferrer

The company recognizes a significant development potential for vafidemstat in psychiatric indications

- Vafidemstat may be a disease modifying therapeutic option for BPD: reduces aggression and produces an overall improvement of the core features of the disease, with no sedation and no weight gain
- BPD prevalence ranges between 0.5%-1.4% of the total population (≤ 9.1M in US+EU5)
- The treatment of BPD is now based on psychotherapeutic interventions. No drugs currently approved for this condition
- A significant unmet medical need
- Global BPD Market, 2018-2027 (US$), $2.6B expected in 2027

- A new Phase IIb in BPD (Portico) under preparation
- Additional Phase IIb in adult aggressive ADHD (Entrance) and ASD (Colonnade) under evaluation
- And if +data in Reimagine-AD, a Phase IIb in AD aggressive patients (Gateway) will be performed
Vafidemstat: a new therapeutic option for aggression in Alzheimer’s disease

Alzheimer’s, the huge need

- 45 million people affected worldwide
- The Global cost of AD is $605 billion/year. No therapeutic options so far
- 20% of the outpatients and 40% of the inmate patients display aggressiveness

Vafidemstat first proposition in AD: a symptomatic drug

- Vafidemstat is safe and highly brain-penetrant in humans
- Brain target engagement in humans established (indirectly)
- Positive effects in different preclinical models on memory, aggression, sociability and apathy, all core features in Mild and Moderate AD patients
- Biomarkers identified that may be surrogate pharmacological biomarkers
- Vafidemstat is pharmacologically active in BPD, ADHD and ASD patients
- Data on aggressiveness in AD to come in December (CTAD-2019 San Diego)

Vafidemstat may also provide clinical benefit in AD either as a single or multi-symptomatic drug or as a disease modifier
ETHERAL: Epigenetic THERapy in Alzheimer’s Disease

Besides aggression, vafidemstat may provide also further benefits to AD patients

An ambitious Phase IIa study to provide useful information to design future Phase II/III studies

- **150 Mild to Moderate AD** patients (6+6 months)
- **Primary Objective:** Safety & Tolerability
- **Secondary Objectives:**
  - Cognition/Agitation/Apathy/Depression/QoL
  - Volumetric MRI
- **Biomarker guided study** (with 8 CSF Biomarkers)

- 117 patients in EU. 17 sites
- Spain, France & UK

- A Twin study in US: around 25-28 patients
- IND approved mid March
- US Sites (3) opened
- FPI recruited in May

**Diagram:**
- Randomization
- MMSE 16-26
  - CSF analysis: Abeta+ P-Tau+
  - MRI at baseline Cogstate at baseline
  - 1.2 mg ORY-2001
  - 0.6 mg ORY-2001
  - Placebo
- Interim Report
- FINAL Report
  - MRI at 6 months
    - Cogstate at 6 months
    - Cognition at 6 months
    - Behaviour at 6 months
    - Biomarkers at 6 months
  - MRI at 12 months
    - Cogstate at 12 months
    - Cognition at 12 months
    - Behaviour at 12 months
    - Biomarkers at 12 months
ETHERAL: Epigenetic THERapy in Alzheimer’s Disease

One of the main goals in ETHERAL is to establish safety of vafidemstat in long-term administration, at therapeutically relevant doses in a frail and elder AD population

Vafidemstat treatment appears so far to be safe and well tolerated:

- Four SAEs were reported in three subjects suspected to be unlikely related to the treatment
- Platelet, neutrophils and other hematological parameters do not show clinically relevant variations due to vafidemstat treatment
- No abnormal and clinically significant liver enzymes levels or other laboratory findings have been reported-to-date

Biomarker and other functional evolution in ETHERAL (blind analysis) is compatible with an informative study

Variations on the S100A9 CSF levels observed in the first 33 patients completing the first 24 weeks of therapy (blind analysis) might be compatible with the preclinical data that shows that vafidemstat decreases S100A9 levels in the CNS. S100A9 is a proinflammatory protein reported to be highly overexpressed in PFC in AD patients

individual patient CSF S100A9 Change from Baseline (CFB) is shown as fold induction after 24 weeks treatment
ladademstat

A Phase II stage clinical compound in Oncology
Iadademstat (ORY-1001): the most advanced selective LSD1 inhibitor in clinic

- LSD1 is involved in different cancers. **High levels of LSD1 often correlate with more aggressive forms of cancer and/or bad prognosis**
- Iadademstat is a small molecule that selectively inhibits LSD1. Preclinical positive *in vivo* results in different xenograft models. Best in Class. Full characterization published in top-rank journal.
- First LSD1i drug to enter into clinical trials. Encouraging results in a FiM Acute Leukemia Phase I/IIa trial

![Cancer Cell Article](oryzoron.com)

**ORY-1001, a Potent and Selective Covalent KDM1A Inhibitor, for the Treatment of Acute Leukemia**

Tamara Maes,1,2,*, Cristina Mascaro,1, Irigo Tirapu,1, Angels Estiarte,1 Filippo Ciceri,1 Serena Lunardi,1 Nathalie Guilbou,1 Alvaro Perdonés,1 Michele M.P. Laffino,1 Tim C.P. Somervaille,1 Dan H. Wiseman,2 Chiangir Davi,3 Ari Melnick,3,4 Christophe Willems,1 Alberto Ortega,1 Marc Martinell,1 Núria Valls,1 Guido Kurz,1 Matthew Fyle,1 Julio Cesar Castro-Palomino,1 and Carlos Busta1

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2Leukaemia Biology Laboratory, Cancer Research UK Manchester Institute, The University of Manchester, Manchester M20 4BX, UK
3Department of Medicine, Division of Hematology & Medical Oncology, Weill Cornell Medicine, New York, 10065 NY, USA
4Department of Pharmacology, Weill Cornell Medicine, New York, 10065 NY, USA
5Drug Development Department (DITEP) and Hematology Department, Gustave Roussy, Université Paris-Saclay, 94805 Villejuif, France
6Lead Contact
*Correspondence: tmaes@oryzon.com
https://doi.org/10.1016/j.ccell.2018.02.002

**Phase I/IIa acute leukemia - previous data**

- Safe and very well tolerated and therefore a meaningful candidate for combination with other agents
- PD Biomarkers identified in different subsets of leukemia
- Antileukemic activity observed in 29% of patients (12/41), including one CRi as Proof of Biological concept
Iademstat a flexible CDP for a Large Market Opportunity

POTENTIAL ONCOLOGICAL INDICATIONS:

Solid Tumors
- Small Cell Lung Cancer
- Prostate cancer
- Colorectal cancer
- Bladder cancer
- Some breast cancers
- Merkel Cell Carcinoma

HemONC
- AML
- MDS
- Myelofibrosis
- Non Hodgkin Lymphoma

Brain/rare Tumors
- Medulloblastoma
- Glioblastoma

MoA well characterized in SCLC, AML and Medulloblastoma
Iademstat in AML: First signs of efficacy

**ALICE:** An AML trial with LSD1i in Combination with azacitidine in the Elderly

A Phase IIa study to evaluate the safety, tolerability, dose finding and efficacy of iademstat (ORY-1001) in combination with azacitidine in older patients with AML in first line therapy

- Single arm & Open label. Up to 36 patients to be enrolled
- **Primary endpoint:** Safety and tolerability of the combo with hypomethylating agent Azacitidine
- **Secondary endpoints:** Responses; time to responses; duration of response; and overall survival

**Preliminary Results**

(5 evaluable patients out of 6)

- Combo well tolerated
- Fast responses (median time to response 1.5 months)
- **80% OR** (4/5 evaluable patients) : **75% CRi** and 25% PR
- 1 patient in CRi with decreasing need of transfusions
- Additional reports to be presented in future Medical Conferences
Iadademstat opportunity in Small Cell Lung Cancer (SCLC)

- LSD1 is a **target well characterized in SCLC** and validated in preclinical models. LSD1 inhibitors are effective in several in-vitro and in-vivo models of SCLC.
- Iadademstat produces **complete and durable tumor regression** in different chemoresistant PDX models.
- Characterized MoA.
- Identified and patented Biomarkers that are differential in sensitive SCLC cell lines, tumors and plasma from patients.
- Phase II trial ongoing in second line SCLC patients using these **biomarkers to stratify patients and identify super-responders**.

---

**Figure:**

- FHSC04

- **Time to reach 6× ITV**

- **P < 0.0001**

- iadademstat

- saline
Iadademstat: SCLC Current Clinical Development Plan

**CLEPSIDRA:** A Combination trial of LSD1 and Etop-Platinum in Small Cell Lung Cancer in biomarker-ID Relapsed patients

A Phase IIa study to assess the safety, tolerability, dose finding and efficacy of iadademstat (ORY-1001) in combination with platinum-etoposide chemotherapy in patients with relapsed, extensive-stage disease small cell lung cancer who are positive to candidate predictive biomarkers

- ✔ Single arm
- ✔ Open label; 4 sites in Spain
- ✔ Up to 36 patients to be enrolled
- ✔ **Primary end point:** Safety and tolerability of the combo with platinum-etoposide therapy
- ✔ **Secondary endpoints:** RECIST responses; time to responses; duration of response; and overall survival

**Current status:**

- ✔ 10 Patients enrolled. One patient at cycle 12
- ✔ Satisfactory and dynamic recruitment pace
Iadademstat: SCLC - CLEPSIDRA - preliminary efficacy signals

**Preliminary Results**

**Case report** from a patient with the longest treatment period in the study presented at IASLC 2019 WCLC:

- Administration of the combination during the first 6 cycles produced a tumor reduction of 78.7% by RECIST criteria
- Subsequent administration of iadademstat alone for four consecutive cycles proved to be safe and well tolerated, without producing any hematological toxicity
- Remarkably, reduction of main lesions and metastasis continues with iadademstat in monotherapy, reaching an overall tumor reduction of 86.3% by RECIST criteria (CT scan evaluation in Cycle 8)

**Preliminary results for first 10 patients enrolled to be presented at ESMO-2019**
Anticipating a rich flow of catalysts / clinical data

**Iademstat Phase IIs in oncology**

- **CLEPSIDRA**
- **ALICE**

**Vafidemstat Phase IIs in CNS**

- **REIMAGINE**
- **ETHERAL**
- **SATEEN**

**2019**

- **Amsterdam; June**
  - AML data

- **Barcelona; Sept.**
  - SCLC data

- **Barcelona; Sept.**
  - SCLC data

- **Orlando; Dec.**
  - AML data

**2020**

- **Chicago; June**
  - SCLC & AML data

- **April; Vienna**
  - AD Global EU 6m data

- **July; Amsterdam**
  - AD Global US 6m data

**Potential Conferences where data may be presented.**
ORYZON – a unique investment opportunity in an epigenetic platform

✔️ A differential proposition in EPIGENETICS drugs in CNS and ONCOLOGY around one of the most interesting targets in the field: LSD1

✔️ 2 molecules in Phase II with promising clinical signals in human patients

✔️ Pioneers in CNS epigenetics

✔️ Vafidemstat shows efficacy in psychiatric disorders (BPD, ADHD, ASD)

✔️ Phase IIb in Borderline personality disorder under preparation. Additional options in ADHD or ASD under evaluation

✔️ Vafidemstat may be also clinically relevant in neurodegenerative disorders (Phase IIIs in MS and AD ongoing)

✔️ Most advanced LSD1i (iadademstat) in Oncology

✔️ 2 Phase II trials ongoing in combo with respective SoC in AML and SCLC

✔️ Positive preliminary efficacy results reported from AML and SCLC trials

✔️ SCLC trial is a biomarker-guided study to stratify responsive patients

✔️ Rich pipeline of clinical news expected in the next 2-4 Qs

✔️ Clinical Operations in US started and under expansion

✔️ A cash efficient company with a seasoned international management team

✔️ €135M market cap. One of the most liquid stocks in the microcap group in MadridSEXC

✔️ Perseverant presence in the US market in the last 4 years. Two successful PIPEs executed in 2018-19 led by US Investment Banks and with participation of US investors

✔️ A public company in Europe with plans to get dual listed in NASDAQ
An experienced and respected managerial team in the Biopharmaceutical industry
Team members have a track record in product discovery & in advancing successfully through product development phases
Demonstrated ability to close world class deals and to lead, and participate in international consortia