Blood procurement:
Process development, clinical trials and the market

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Manufacturing and economic model
Teaching your cells to treat your disease

ASTriA: from Blood Sample to Medicinal Product

Blood collection

1. Blood collection
2. Natural presence of Treg ( )
3. Stimulation with antigen (Ag) ( )
4. Isolation of Ag-specific Treg
5. Industrial expansion of Ag-Treg
6. Drug (ATMP in EU)

Off the shelf
5 years stability data

Exceptional value proposition

Logistic and cost effectiveness: key success factors in chronic diseases
- Starting material simple to collect
- Targeting product availability 5 weeks after prescription (Phase III and commercial)
- Several years treatment doses
- Convenient frozen central and local storage

One blood sample, One processing, Multiple years of personalized treatment
First generation
*Autologous cell therapy*

Next generation – Target Product Profile
*Hybrid autologous and allogeneic therapy*

**Gross Margin**

- **Autologous Model**
  - GM ~40-60%

- **Hybrid Autologous Model**
  - GM ~80-85%

**Hybrid autologous model – Gross Margin target ~80-85% in line with biological products**
TxCell to bring its unparalleled Treg expertise to continue controlling process development/improvement

<table>
<thead>
<tr>
<th>Before 2015</th>
<th>Since 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing Process</td>
<td>Proprietary GMP validated process and GMP-proving laboratory</td>
</tr>
<tr>
<td>Phase I &amp; II Production</td>
<td>CMO (UK) New process development &amp; Phase III readiness</td>
</tr>
<tr>
<td>Upcoming Phase III &amp; Commercial Production</td>
<td>CMO, Europe TT ongoing ready Q2 2016</td>
</tr>
<tr>
<td></td>
<td>CMO, United States Pre-TT evaluation</td>
</tr>
<tr>
<td></td>
<td>Asia TT in 2017 or 2018</td>
</tr>
<tr>
<td></td>
<td>CMOs EU, US, Asia TT in 2017-2018</td>
</tr>
</tbody>
</table>

Going « fabless » while providing significant resources to process improvement and new process development
Development pipeline
### Product Pipeline

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication(s)</th>
<th>Research</th>
<th>Preclinical</th>
<th>Phase I/II</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASTrIA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ovasave® (Ova-Treg)</td>
<td>Crohn's Disease, IBD</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Col-Treg</td>
<td>Non Infectious Uveitis</td>
<td></td>
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</tr>
<tr>
<td>Myelin-Treg</td>
<td>Severe CNS diseases</td>
<td></td>
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<tr>
<td>Des-Treg</td>
<td>Severe Skin diseases</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>ENTrIA</strong></td>
<td></td>
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</tr>
<tr>
<td>ENTX#BP</td>
<td>Severe Skin diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENTX#DN</td>
<td>Lupus Nephritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENTX#MY</td>
<td>Severe CNS diseases</td>
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</tr>
</tbody>
</table>
Few therapeutic solutions offering limited efficacy, resistance and tolerability issues

Crohn’s Disease Activity

« Remission »

1st Line: Steroids
2nd Line: Immunosuppressors
3rd Line: Biologics
4th line: Type 1 Treg cells: Ovasave®

<table>
<thead>
<tr>
<th>STEROIDS</th>
<th>IMMUNOSUPPRESSORS</th>
<th>BIOLOGICS</th>
<th>OVASAVE®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>+</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Tolerability</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Annual cost ≥€22,000

Value-added Premium

74,000 to 100,000 refractory patients → Potential market estimated at over €2.2bn

1. GlobalData 2014
2. Company estimate for 8 majors markets (US, France, Germany, UK, Spain, Italy, Canada, Japan), based on the total number of patients suffering from Crohn’s disease and taking anti-TNF drugs (GlobalData 2014) and the rate of patients non-responsive to anti-TNF treatment (Roda G. et al. 2016, in Press, doi:10.1038/ctg.2015.63)
3. Company estimate, based on the estimated number of refractory patients and the selling price of current last line biologic treatments
Teaching your cells to treat your disease

Phase I/II: Compelling clinical results in efficacy, safety and durability

- 20 patient-study in 4\textsuperscript{th} line, refractory Crohn’s Disease
- Good tolerability of Ovasave\textsuperscript{®} (autologous ovalbumin-specific Tregs)
- High response and remission rate with dose related efficacy at 5 to 8 weeks after single injection
- Biomarkers for identification of patient responses
- Physicians’ assessments lead to repeated injections for up to 1 year
- Phase I/II retreatments document feasibility and tolerability of multiple injection
- Full study results published in Gastroenterology and featured in Nature Reviews of Gastroenterology (2012)

- Strong set of data supporting transition to Phase IIb
- Open IND & Fast Track Designation in US

Percentage of patients receiving 10\textsuperscript{6} cells in Response or Remission on CDAI (Crohn’s Disease Activity Index) (n=8)

<table>
<thead>
<tr>
<th>Week 5</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response: ( \Delta \text{CDAI} \geq 100 )</td>
<td>Remission: ( \leq 150 ) CDAI points</td>
</tr>
<tr>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>38%</td>
<td>25%</td>
</tr>
</tbody>
</table>

CDAI* change from baseline – Dose 10\textsuperscript{6} (n=8)

-300 -200 -100 -50 0 50 100 150 200

Weeks
Ongoing Phase IIb CATS29 Study in Crohn’s Disease: Phase IIb Study Design

- Randomized placebo-controlled study
- 29 centers in 6 European countries (extendable to US with open IND)
- 56 patients with moderate to severe refractory Crohn’s disease (CDAI >250)
- 32-week treatment split into two phases
  - Blinded phase (8 weeks): patients will receive either placebo or Ovasave® $10^6$ (randomized 1:1) at week 0
  - Unblinded phase (24 weeks): all patients will receive Ovasave® $10^6$ (three further open label injections at 8-week intervals)
- Enabling dose-finding and Phase III studies
- European regulatory approval to restart study expected in Q2 2016 through VHP process
  - US IND to be amended accordingly
- Trial resumption expected upon availability of funds
  - Topline data expected within 18-21 months of trial resumption

Confirming the Proof of Concept in Refractory Crohn’s Disease

Primary endpoint assumption: 70% response with Ovasave® $10^6$ vs. 30% on placebo
Presentation Overview
Why materials from patients and healthy donors are needed for the pharmaceutical development of autologous cell therapies in inflammatory diseases?

- Impact of donor variability
- Potential impact of patient’s condition
- Strategy for manufacturing process development

What are the challenges and the regulatory pathway to obtain such human materials in France?

- French regulatory framework
- Pathway to regulatory approvals
- Logistics for the research
- Blood procurement from healthy volunteer

The procurement of patient materials and related logistic remain a challenge, even once clinical trials are authorised: some suggestions to overcome them in Europe
Product comparability
Healthy donor vs Patient materials

Starting materials with donor variability

Donor materials

1. Functionally altered cell population
2. Low frequency of cells of interest
3. Altered identity features

Potential impact on manufacturing process, on product characteristics
Healthy donor vs Patient materials

Starting materials with donor variability

Manufacturing process

Drug Products with defined key attributes

Donor materials
1
2
3
4

DP
Healthy donor vs Patient materials

Starting materials with donor variability

1. Healthy donor materials
2. Patient materials
3. 1
4. 2

Manufacturing process

Immunosuppressants
Steroids

Drug Products with defined key attributes

DP

Disease characteristics
Healthy donor vs Patient materials

Starting materials with donor variability

Healthy donor materials

Patient materials

Manufacturing process

Drug Products with defined key attributes

1
2
3
4

DP

DP
Healthy donor vs Patient materials

Starting materials with donor variability

Manufacturing process

Drug Products with defined key attributes

Healthy donor materials

Patient materials

Comparability on key attributes

Potential impact
# TxCell study case – Healthy vs Patient donor / Phase I/IIa vs Phase IIb process

Comparability analysis of cytokines secretion potential of Ova-Treg cells

<table>
<thead>
<tr>
<th>Cytokine secretion</th>
<th>Phase I/IIa</th>
<th>Phase IIb</th>
<th>Comparability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD (n=50)</td>
<td>HD (n=17)</td>
<td>CD (n=4)</td>
</tr>
<tr>
<td>ΔIL-10 (pg/ml)</td>
<td>662.7 ± 126.5</td>
<td>214.6 ± 74.6</td>
<td>6327 ± 1179</td>
</tr>
<tr>
<td>IL-10 (ng/ml)</td>
<td>11.6 ± 0.69</td>
<td>13.4 ± 4.1</td>
<td>38.1 ± 6.5</td>
</tr>
<tr>
<td>IL-4 (ng/ml)</td>
<td>0.1 ± 0.0</td>
<td>0.3 ± 0.10</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>IFNγ (ng/ml)</td>
<td>2.6 ± 0.7</td>
<td>0.7 ± 0.22</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>IL-13 (ng/ml)</td>
<td>7.63 ± 1.3 (n=47)</td>
<td>26.4 ± 4.57</td>
<td>32.8 ± 6.3</td>
</tr>
</tbody>
</table>

### TxCell study case – Healthy vs Patient donor / Phase I/IIa vs Phase IIb process

Comparability analysis of surface & intracellular molecules expression on Ovasave (DP)

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Phase I/IIa Cats1 (n=20)</th>
<th>Phase I/IIa HD (n=9)</th>
<th>Phase IIb CD (n=4)</th>
<th>Phase IIb HD (n=12)</th>
<th>Comparability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treg markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD25</td>
<td>32.9 ± 18.7 (6.8-66.6)</td>
<td>41.8 ± 37.2 (3.8-92.3)</td>
<td>85.8 ± 3.4 (76.2-92.5)</td>
<td>88.1 ± 10.4 (65-98.3)</td>
<td>Increased mean expression with phase IIb process overlapping with phase I/IIa data</td>
</tr>
<tr>
<td>CD62L</td>
<td>1.3 ± 1.2 (0.1-4.2)</td>
<td>2.2 ± 1.9 (0.8-6.3)</td>
<td>0.5 ± 0.1 (0.2-0.8)</td>
<td>0.8 ± 0.5 (0.4-2.1)</td>
<td>Yes</td>
</tr>
<tr>
<td>CD127</td>
<td>1.1 ± 1 (0.1-3.7)</td>
<td>2.9 ± 3.1 (0.7-9.8)</td>
<td>0.6 ± 0.3 (0.2-1.3)</td>
<td>0.4 ± 0.1 (0.3-0.5)</td>
<td>New Release crit with full comparalt</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>0.4 ± 0.7 (0.03-2.9)</td>
<td>10.8 ± 11.4 (0.1-27.8)</td>
<td>5.3 ± 2.1 (1.5-10.8)</td>
<td>2.5 ± 2.3 (0.1-7.8)</td>
<td>Yes</td>
</tr>
<tr>
<td>GITR</td>
<td>6.7 ± 4.9 (0.3-16.9)</td>
<td>19.6 ± 17.8 (0.9-54.1)</td>
<td>42.7 ± 4.7 (35.6-56.3)</td>
<td>46.7 ± 15.7 (27.1-77.3)</td>
<td>Increase mean expression with phase IIb process overlapping with phase I/IIa data</td>
</tr>
<tr>
<td>Suppressive molecules</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CD39</td>
<td>68.9 ± 36.4 (4.5-100)</td>
<td>79.9 ± 30.3 (6.4-99.8)</td>
<td>62.2 ± 22.0 (17-100)</td>
<td>70.8 ± 41.7 (4.3-99.9)</td>
<td>Yes</td>
</tr>
<tr>
<td>CD49d</td>
<td>74.9 ± 5.5 (51.5-99)</td>
<td>ND</td>
<td>32.3 ± 5.9 (20.1-44.3)</td>
<td>66.7 ± 13.2 (35.3-89) (n=3)</td>
<td>Batch heterogeneity in all products types leading to different mean expression of CD49d</td>
</tr>
<tr>
<td>CD20</td>
<td>93.2 ± 1.4 (82.5-99.5)</td>
<td>ND</td>
<td>76.6 ± 6.5 (65-95.1)</td>
<td>93.8 ± 1.9 (91-98.5) (n=3)</td>
<td>Yes</td>
</tr>
<tr>
<td>Granzyme B</td>
<td>44.6 ± 27.2 (4.96.8)</td>
<td>99.7 ± 0.45 (99.7-100)</td>
<td>100±0.02 (99.9-100)</td>
<td>99.7 ± 0.3 (98.4-100)</td>
<td>Comparability of products with both processes performed on healthy donors</td>
</tr>
<tr>
<td>PD-1</td>
<td>2.4 ± 1.5 (0.4-5.3)</td>
<td>4.8 ± 3.1 (0.9-9.9)</td>
<td>12.2 ± 8.1 (1.3-20.7)</td>
<td>3.7 ± 0.2 (0.9-13.8)</td>
<td>Yes</td>
</tr>
<tr>
<td>Homing molecules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFA-1</td>
<td>99.4 ± 0.8 (97.3-100)</td>
<td>99.6 ± 0.5 (98.5-100)</td>
<td>99.5 ± 0.1 (99.4-99.7)</td>
<td>97.2 ± 2.6 (90.1-98)</td>
<td>Yes</td>
</tr>
<tr>
<td>PSGL-1</td>
<td>77.2 ± 15.5 (46.7-97.7)</td>
<td>46.1 ± 25.5 (3-90.5)</td>
<td>95.3 ± 1.1 (92.5-97.8)</td>
<td>84.9 ± 23.2 (15-100)</td>
<td>Increased mean expression with phase IIb process overlapping with phase I/IIa data</td>
</tr>
<tr>
<td>CD49d</td>
<td>74.9 ± 5.5 (51.5-99)</td>
<td>ND</td>
<td>32.3 ± 5.9 (20.1-44.3)</td>
<td>66.7 ± 13.2 (35.3-89) (n=3)</td>
<td>Batch heterogeneity in all products types leading to different mean expression of CD49d</td>
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<tr>
<td>CD20</td>
<td>93.2 ± 1.4 (82.5-99.5)</td>
<td>ND</td>
<td>76.6 ± 6.5 (65-95.1)</td>
<td>93.8 ± 1.9 (91-98.5) (n=3)</td>
<td>Yes</td>
</tr>
<tr>
<td>Integrin β7</td>
<td>38.5 ± 38.1 (1.6-99.8)</td>
<td>32.1 ± 21.8 (17.5-70.4) (n=5)</td>
<td>0.7 ± 0.4 (0.1-1.9)</td>
<td>7.9 ± 5.6 (2.2-18.2)</td>
<td>Decreased mean expression with phase IIb process overlapping with phase I/IIa data</td>
</tr>
<tr>
<td>Th17 surface marker</td>
<td>IL-23Rα</td>
<td>6.3 ± 2.2 (3-10.5)</td>
<td>1.7 ± 0.1 (n=2; 1.6-1.8)</td>
<td>6.1 ± 1.4 (3.8-9.6)</td>
<td>5.4 ± 0.8 (4.5-8.4)</td>
</tr>
</tbody>
</table>

- **Increased mean expression with phase IIb process overlapping with phase I/IIa data**
- **New Release crit with full comparalt**
- **Comparability of products with both processes performed on healthy donors**
- **Increased mean expression with phase IIb process overlapping with phase I/IIa data**
- **Batch heterogeneity in all products types leading to different mean expression of CD49d**
Conclusion:

Preferred strategy to develop a robust manufacturing process should be:

- Development on healthy donor materials
- Validation of the feasibility with patient materials
- Comparison of products and process between healthy donors and patients
- Evaluation of the benefit/risk of each difference observed

Objective of manufacturing process development: obtain a product at least as good as the previous one
Teaching your cells to treat your disease

Patient material procurement in France
French regulatory framework:

- “Procurement, preparation, use and storage of human body parts for scientific purposes”, also called “Biological sample collection”
  (French Public Health Code, Articles L1243-3, R1243-49 and followings)
- Apply to blood, cells and tissues, from healthy donor and patients
- Use of human materials for its own researches
  ➔ Declaration of the activities
- Use of human materials / collection of biological samples for transmission to another institution
  ➔ Request for authorisation
- Regulatory pathway through:
  o French Ministry of Research “Ministère de l’Enseignement Supérieur et de la Recherche”
  o Ethics Committees
Pathway to regulatory “approvals”:

• Fill-in dossier for "scientific research on human materials":
  
  o Identity of the responsible of the scientific activity(ies)
  o Description of the facilities & equipment to be used for the scientific activity
  o Description of the biological sample collection constituted and used
  o Scientific rationale for the research
  o Description of modalities of the donor information
    + If personal data are collected: Statement of compliance to the standards for personal data protection (declaration to the CNIL)
    + If preparation of products for therapeutic purposes on the same site: Methods used to avoid cross-contamination
Pathway to regulatory “approvals”:

• Declaration to the Ministry of Research:
  o Dossier to be sent on line
  o Validation of the dossier: 1 month
  o Tacit agreement: 2 months

• Submission to Ethics Committee:
  o Dossier + short protocol & patient’s informed consent
  o Submission in parallel to the Ministry of Research
  o EC opinion within 35 days of submission

• For health establishments only:
  o Additional submission to Regional Health Agency “Agence Régionale de Santé”

⇒ Useful to have previous discussion with the authorities
⇒ Research allowed to start 3 months after submission
Logistics for the scientific research ➔ As for a “mini-clinical trial”

- Identify sites for procurement of human materials:
  - Adequate site authorisation
  - Physician willingness
- Establish contracts
- Choice of the relevant EC

Specific example of blood procurement from healthy volunteers in France

- Only blood establishments are authorised to provide blood (EFS)
- Frequently standard blood bags not suitable for therapeutic purpose ➔ Limited availability
- Import foreign blood (including from EU): authorisation to be requested to French competent authority (ANSM)
Conclusion: Procurement of human materials to be used for the pharmaceutical development in France

• Regulatory pathway:
  o “Preparation and storage of human body parts for scientific purposes” also called “human biological samples collection”
  o By the Research Ministry and an Ethics Committee
  o Around 3 months between dossier submission and research start

• Similar to a “mini-clinical trial”:
  o Identification of procurement site(s)
  o Establishment of contract with hospital/physician
  o Writing of short research synopsis and patient informed consent
  o Strategic choice of the EC
  o Insurance to be contracted
  o CNOM declaration if relevant for the sponsor of the research
  o …
Procurement for a Clinical Trial in Europe
Starting materials procurement for manufacture of clinical batches:

• Regulated in Europe through EU Directives:
  • 2002/98/EC (for blood)
  • 2004/23/EC (for tissues/cells)
  • Plus legislation implementation across EU member states

• Authorisation for procurement independent from clinical trial authorisation

ès Clarify, in each country:
  o Category of the starting materials
  o Kind of authorised establishments
  o Criteria for biological qualification
### TxCell study case - European phase II clinical trial: Applicable regulation

<table>
<thead>
<tr>
<th>Member States</th>
<th>Blood Dir. 2002/98/EC</th>
<th>Tissues-Cells Dir. 2004/23/EC</th>
<th>National specificities</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>✓</td>
<td>✓</td>
<td>Procurement at the hospital or blood establishment</td>
</tr>
<tr>
<td>Belgium</td>
<td></td>
<td>✓</td>
<td>Procurement at the hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tissue establishment involved for testing &amp; release of the sample before shipment to manufacturing site</td>
</tr>
<tr>
<td>UK</td>
<td>✓</td>
<td>✓</td>
<td>Blood establishments not willing to sample patients; eventually procurement through tissue establishment authorised by MHRA an HTA (case by case decision)</td>
</tr>
<tr>
<td>Germany</td>
<td>✓</td>
<td>✓</td>
<td>Procurement at the hospital</td>
</tr>
<tr>
<td>Italy</td>
<td>✓</td>
<td></td>
<td>Procurement at the hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Written agreement to define responsibilities (site vs manufacturer)</td>
</tr>
<tr>
<td>Austria</td>
<td>✓</td>
<td></td>
<td>Procurement in a blood establishment (§14 Blood Safety Act &quot;Blutsicherheitsgesetz&quot;)</td>
</tr>
</tbody>
</table>
Procurement for CT in Europe

TxCell study case - European phase II clinical trial: Logistics set-up

Define for each investigational site involved in the trial:

- An establishment authorised for procurement
  - Close to the site
  - Willing to do the sampling
  - Establish contract

- The associated logistics
  ➔ more complex organisation with additional entities involved in the trial
Conclusion: Procurement of patient materials for clinical supply

- Non harmonised application of EU Directives 2002/98/EC (for blood) and 2004/23/EC (for tissues/cells)
- Authorisation for procurement not linked to clinical trial authorisation

→ Need to clarify applicable regulation and set-up logistics:
  - In each country
  - At each investigational site

→ Anticipate procurement well in advance of the start of a clinical trial & be prepared to flexibility and adaptation
• Dossier for scientific research on human materials:
  https://appliweb.dgri.education.fr/appli_web/codecoh/IdentCodec.jsp

• French Public Health Code:
  - Article L1243-3:
    http://www.legifrance.gouv.fr/affichCodeArticle.do?cidTexte=LEGITEXT000006072665&idArticle=LEGIARTI000006686220&dateTexte=20090501
  - Articles R1243-49 and followings:
    http://legifrance.gouv.fr/affichCode.do;jsessionid=1ED9955A6831A660AD2620947230C00B.tpdila12v_2?idSectionTA=LEGISCTA000006196227&cidTexte=LEGITEXT000006072665&dateTexte=20150923

• Guideline on comparability of biotechnology-derived products after a change in the manufacturing process – Non-clinical and Clinical issues:
Thank you!