ChondroCelect®

First ATMP approval in Europe

Innovation in Healthcare – Brussel 20 May 2010

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Overview

- Introduction
- European regulatory framework
- The ChondroCelet experience
- Other considerations
- Conclusions
Focus
Regenerative medicine - Innovative local treatments for damaged and osteoarthritic joints

Products
- **ChondroCelect**®, autologous cell-based product for cartilage repair. *First approved ATMP in Europe*
- **Chondromimetic™**, resorbable implant for treatment of osteochondral defects. *Approved in Europe (CE)*

Pipeline
Complementary regenerative medicine products, integrating biomaterials and adult stem cells

Locations
HQ in Leuven (Belgium); Manufacturing in Leuven and Memphis (US); Cambridge (UK)

Finance
Listed on NYSE Euronext since March ‘07
Focus: regenerating motion, joint function

Cartilage defects
- > 2 million articular cartilage defects diagnosed per year*
- Ca. 130,000 grade 3-4 full thickness defects*

Meniscus trauma
- 2.2 million menisci removed or partially removed per year*

Osteoarthritis
- 2.5 to 5% of adult population in Western world has symptomatic knee osteoarthritis

* Europe and US
ChondroCelect®

- Controlled manufacturing
- Biopsy
- Cartilage defect
- Implantation
- Repair tissue

TiGenix® REGENERATING MOTION
ATMP : European regulatory framework

- ATMP have to comply with two European regulatory frameworks
  - Medicinal Products Directives and the new ATMP Regulation
  - SANCO Directives

- ATMP Regulation
  - Lex specialis on Dir 2001/83/EC (Medicinal Products Directive)
  - Regulation 1394/2007/EC, of application since 30 Dec 2008
  - Developed for regulating new and complex (advanced) therapies
  - Principle: ATMP are also medicinal products and have to prove safety and efficacy before being put on the market
  - Market Authorization Application to prepare and to submit to the EMA
SANCO regulatory framework

- Three Sanco Cell and Tissue Directives
  - 2004/23/EC: setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
  - 2006/17/EC and 2006/86/EC: technical specifications

- Transposed in “27” national legislations

- Operational Sanco models
  - Germany: P and T license, full license; 16 Länder
  - The Netherlands: no P licences; Weefselinstellingen en Orgaanbank
  - Belgium: P license for Productie-instelling (autologous)
  - In summary: a patchwork…
### SANCO vs ATMP

<table>
<thead>
<tr>
<th>Tissues and cells intended for human application</th>
<th>Directive 2004/23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufactured products derived from animal tissues and cells and intended for human use ruled by another European legislation</td>
<td>Regulation 1394/2007 and Directive 2001/83</td>
</tr>
<tr>
<td>Tissues and cells intended for scientific research</td>
<td>Directive 2004/23</td>
</tr>
<tr>
<td>With human application</td>
<td>Other legislations</td>
</tr>
<tr>
<td>Without human application</td>
<td></td>
</tr>
</tbody>
</table>

Source: Marc Martens, Bird&Bird
ATMP and the Regulations

- ATMP: innovative medicinal products
  - Broad range of products (e.g. somatic cells, tissue engineered products, combination products (with medical devices))
  - Science still evolving (many unknowns)
  - Often non-classical therapy approach (e.g. including surgery)
  - Little regulatory experience
    - No or small number of benchmark products
    - New, evolving regulations
Filing ChondroCelect as ATMP in Europe

- Central submission at EMA

- Market authorization application (file)
  - Quality (product manufacturing and quality control)
  - Non-Clinical (safety and proof of concept)
  - Clinical (safety and efficacy in humans)
  - Risk management

- Reviewed at EMA (Rapporteur, Co-Rapporteur, CAT, CHMP)

- Approved by European Commission (Market Authorization)
ChondroCelect development challenges

- **CMC requirements**
  - Consistent manufacturing - complex and autologous composition
  - Stringent product release criteria – relevant tests

- **Non-clinical data**
  - Animal model - rejection of the xenograft, different biology of the cells and the joint
  - Long term efficacy – problems in rehabilitation

- **Clinical design**
  - Randomized controlled trial
  - Relevant clinical read-outs
  - Duration of the trial
  - Safety of the product vs the procedure
Potency: proprietary molecular profile of stable cartilage forming cells

Comparison of cell populations that pass and fail proprietary in-vivo assay on gene expression profiles

150 positive markers

Stable cartilage

60 negative markers

Non-stable cartilage

ChondroCelect® markers

Del’Accio et al., A & R, 2001
Goat model: proof of principle
(Repair tissue after 10 weeks in goat model – Toluidine blue)

- Phenotypically stable chondrocytes
- Dedifferentiated chondrocytes
- Dermal fibroblasts
ChondroCelect clinical picture

Overall KOOS\(^{(1)(2)}\)

Longitudinal analysis: treatment effect at 36m (mixed linear model)

<table>
<thead>
<tr>
<th>KOOS</th>
<th>P-value (3)</th>
</tr>
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<tbody>
<tr>
<td>Overall*</td>
<td>0.048</td>
</tr>
<tr>
<td>Pain</td>
<td>0.064</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.044</td>
</tr>
<tr>
<td>Activity (ADL)</td>
<td>0.123</td>
</tr>
<tr>
<td>Sports</td>
<td>0.123</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Treatment failures (reinterventions)
CC: 2     MF: 7

(1) Knee Injury and OA Outcome Score - Average of all KOOS domains, except Sports
(2) Full Analysis Set excluding treatment failures and without imputation for missing data
(3) Time as a categorical value
ChondroCelect Marketing Authorisation

- **Quality**
  - Robust and validated manufacturing process
  - Product quality attributes and product characterisation

- **Safety**
  - Adverse events ‘as expected’
  - No major safety risks identified
  - Risk management strategy in place

- **Efficacy**
  - Structural superiority
  - Demonstrated clinical benefit

- Positive benefit/risk assessment
First advanced therapy product approved in EU

European Medicines Agency
Press office

London, 26 June 2009
Doc. Ref. EMEA/CHMP/394741/2009

PRESS RELEASE
European Medicines Agency recommends first marketing authorisation for an advanced therapy medicinal product

The European Medicines Agency has recommended the first marketing authorisation for an advanced therapy medicinal product, following a positive opinion from the Agency’s Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP).

REGULATED INFORMATION
OCTOBER 6, 2009

ChondroCelect approved in Europe

Leuven (BELGIUM) – October 6, 2009 – TiGenix (NYSE EURONEXT BRUSSELS: TIG) announced that it has received approval from the European Commission for ChondroClect as the first Advanced Therapy Medicinal Product.
EU filing of ChondroCelect: RA experience

- First ATMP to go the whole way (central procedure)
- Flexible and realistic review process
  - ChondroCelect entered as a SCT
  - “In process” implementation and application of the new ATMP regulation
  - CAT joined the ongoing process
  - On purpose SAG
  - Clock stops
  - Rapid implementation of new guidance (ATMP risk management)
- Understand and comply with the requirements for Q S E
- Maintain a continuous dialogue with the regulatory agency to anticipate regulatory expectations in an evolving medicinal field
Post-marketing phase

- Regulatory aspects
  - Post-marketing commitments and follow up measures
  - Risk management plan
  - Periodic Safety Updates

- Product improvement
  - Manufacturing experience
  - New developments

- Clinical aspects
  - Increase clinical database, now in the “real life” setting
  - Document long-term function restoring (regenerative medicine)
Other reflections - Reimbursement

- Product approval is central (EMA, EC)
- Reimbursement is a national matter
  - 27 EU countries, thus “27” mechanisms to manage
  - “27” health care priority settings to manage
- Reimbursement expectations
  - QALY, durability, comparative effectiveness
  - “Value for money”
- “Innovation-supportive” reimbursement mechanisms
  - Risk sharing, performance based pricing
  - “Start-up” mechanisms (e.g. NUBs)
Other reflections - SME

- SME profile
  - Innovative developments
  - Entrepreneurial
  - Small, medium sized

- SME challenges
  - Expertise highly focused and consequently limited
  - Limited resources (collaborators, finances, “time”)
  - No pipeline fallback position

- SME support
  - EMA SME office
  - Adapted and sustainable financing
Conclusions

- It is possible to get ATMPs licensed, see ChondroCelect
- Know, comply with, and meet the regulatory requirements
  - ATMP Regulation, SANCO Directives
  - Quality, Safety, Efficacy standards
- Early and regular contacts with the Regulatory Authorities
  - Scientific Advices
  - SME Office
- Realize that there is also the “Fourth Hurdle”
- Be a performant and realistic SME
  - Select “your best path”
  - Make sure the financing is OK
Thank you for your attention

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