ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPs) IN EUROPE 8 YEARS ON: WHAT IS THE PATH TO MARKET ACCESS SO FAR?

Dellamano R[1], Mycka J[2], Lobb W[2], Dalal N[2], Dellamano L[1], Mora M[2], Liguori G[1]

[1]ValueVector, Milan, Italy; [2]Medical Marketing Economics, LLC, Montclair, NJ, USA,

Objectives

- To examine the current EU5 market access landscape for ATMPs.

Methods

- Assessed the regulatory path, HTA assessments and funding mechanisms for ATMPs

Methods (cont'd)

- Examined all ATMPs from Chondrocelect which was the first approved ATMP by the European Commission (EC) in October 2009 to Zalmoxis recently approved in September 2016
- Reviewed market access status of ATMPs across the EU5 based on listings in national price databases and assessment from national HTA agencies such as the HAS (France), GBA (Germany), AIFA (Italy) and NICE/SMC (UK)
- Examined time to market for all ATMPs across the EU5

Results

- Eight ATMPs have been approved by the EC as of September 2016 (Table 1a and Table 1b)
  - Germany has a dual regulatory requirement as authorization needed from Paul Ehrlich Institute (PEI)
- Of the approved ATMPs, two are no longer available and the third will be withdrawn later this year
  - Market authorization was suspended for MACI (matrix-induced autologous chondrocyte implantation) based on CHMP recommendation
  - Market authorization was withdrawn for Provenge (sipuleucel-T) upon the request of the marketing authorization holder
  - Market authorization will be withdrawn for Chondrocelect (characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins) as of November 30, 2016 for commercial reasons
- Glybera (alipogene tiparvovec), the first gene therapy to be approved by the EC (2012), a hospital use only drug in Germany with reimbursement negotiated by the hospital and sickness funds on a case by case basis, is not reimbursed in any of the other EU4 markets
  - Ex-factory cost of treatment is €984,000 (Germany) and £693,000 in the UK (70kg patient, 24 vials used)
- Holoclar (Ex vivo expanded autologous human corneal epithelial cells containing stem cells), a more recent approval (2016), is an interesting case study of an ATMP that has been classified as a procedure by the GBA in Germany and therefore bypassed AMNOG assessment
  - It is not yet marketed/commercialized in the other EU4 markets where negotiations are ongoing
- Imlygic (talimogene laherparepvec), is the only ATMP assessed and recommended for use in the UK by NICE under a PAS
  - Not reviewed by the SMC (none of the ATMPs on the market have been reviewed by SMC as of September 2016)
- Strimvelis (autologous CD34+ cells transduced to express ADA) is a unique case in terms of pricing (only one price, valid wherever the patients come from) and reimbursement (payment by results and payment by instalments in Italy, with other countries likely to negotiate similar conditions) and could represent a new model for ATMPs
- Zalmoxis (genetically modified allogeneic T cells) is the latest ATMP approved by the EMA but is not yet commercially available in any EU country

Table 1a - EC approval and indications for ATMPs on the market as of September 2016

Brand	Generic description	EC approval	Indication
Chondrocelect*	Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	October 5, 2009	Repair of single symptomatic cartilage defects of the femoral condyle of the knee (ICRS grade III or IV) in adults
Glybera	Alipogene tiparvovec	October 25, 2012 (exceptional circumstances)	For adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions
Holoclar	Ex vivo expanded autologous human corneal epithelial cells containing stem cells	February 17, 2015 (conditional approval)	Treatment of adult patients with moderate to severe limbal stem-cell deficiency due to ocular burns
Imlygic	talimogene laherparepvec	December 16, 2015	Treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease
Strimvelis	autologous CD34+ cells transduced to express ADA	May 26, 2016	Treatment of ADA-SCID (severe combined immunodeficiency due to adenosine deaminase deficiency)
Zalmoxis	allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	August 18, 2016 (conditional approval)	Adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies

*To be withdrawn from the market on November 30 2016

Table 1b - EC approval and indications for ATMPs withdrawn/suspended as of September 2016

Brand	Generic description	EC approval	Indication
Maci	Matrix-applied characterized autologous cultured chondrocytes	June 26, 2013 (MA suspended since Sep 2014 due to closure of EU manufacturing site)	Repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the Modified Outerbridge Scale) of 3-20cm² in skeletally mature adult patients
Provenge	Autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T)	September 6, 2013 (MA withdrawn on May 19, 2015 at the request of the MA holder for commercial reasons)	Treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated

Table 3 - Strimvelis - a new/unique model for P&R of ATMPs

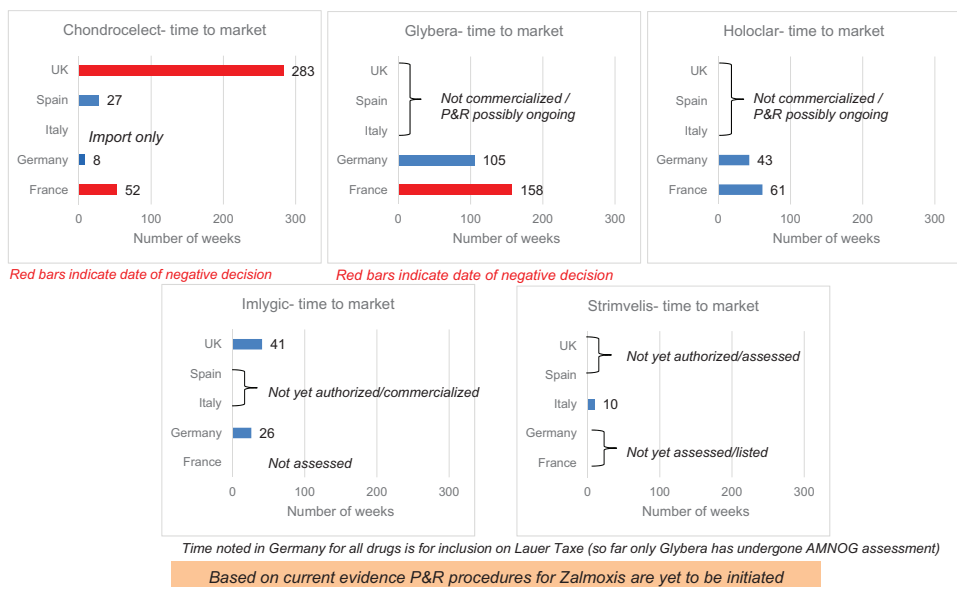
- *Strimvelis is a one time treatment for ADA-SCID, also known as bubble boy disease- 15 patients are expected across Europe*
- *Strimvelis can only be administered at the San Raffaele hospital in Milan, Italy, which means families have to travel for treatment*
- *Because of this the approved Italian price is the de facto price for all patients (€594,000)*
  - *In Italy, payment by results/staggered payment model has been negotiated*
- *Reimbursement decisions in other countries likely to be made on a case by case basis as patient travel would need to be authorized*

"The company was considering different models" on pricing. Those models could include staggered payments--which are part of the Italian deal now--and outcomes-based arrangements….
…If a patient needs to go back onto a different therapy down the line, or if their health declines, we will look at refunding some of the cost"- GSK

Table 2 - Market access status of EC approved ATMPs on the market as of September 2016

Brand	France	Germany	Italy	Spain	UK-NICE
Chondrocelect	Assessed by TC but reimbursement not granted	Listed in the Lauer-Taxe for hospital use only since Dec 1, 2009 Was initially available through NUB but no longer reimbursed	Not authorized; however hospitals can import it	Spanish authorization April 15, 2010 Commercialized, hospital use only, risk sharing agreement negotiated	Preliminary recommendation: to be used in research only
Glybera	Assessed by TC but reimbursement not granted	Listed in the Lauer-Taxe since November 1, 2014; Hospital use only since October 15, 2015. Non quantifiable additional benefit; temporary assessment, set to expire June 1, 2017	Not authorized yet; CTS is assessing clinical data as of September 2016	Spanish authorization 10-October-2014; Not yet commercialized	Not routinely commissioned- no assessment published
Holoclar	Assessed by TC (ASMR IV; 65% proposed reimbursement) but not marketed yet	Listed in the Lauer-Taxe since December 15, 2015; hospital use only; Not considered as a new drug but as part of a new procedure; no dossier requested	Authorized as Class C-nn drug on February 15, 2016 P&R negotiation ongoing	Spanish authorization September 16, 2015 Not yet commercialized	NICE proposed HTA (draft scope published pre-referral)
Imlygic	Not been assessed yet by the Transparency Committee	Listed in the Lauer-Taxe since June 15, 2016. G-BA final evaluation expected by mid December 2016	Not authorized	Spanish authorization January 22, 2016. Not yet commercialized	Recommended by NICE with restrictions and PAS
Strimvelis	Not been assessed yet by the Transparency Committee	Not listed in the Lauer-Taxe as of September 21, 2016 Authorized by the Paul Ehrlich Institut (PEI)	Hospital only drug; Restricted Prescription; Patients registry; AIFA Innovative Status; 1-year Payment By Results**; reimbursed price paid by instalments (amount is confidential)	Not authorized yet	Not assessed by NICE
Zalmoxis	Not yet commercialized in any country				

Figure 1 - Time to national market access decisions of EC approved ATMPs on the market as of September 2016



Time noted in Germany for all drugs is for inclusion on Lauer Taxe (so far only Glybera has undergone AMNOG assessment)

Based on current evidence P&R procedures for Zalmoxis are yet to be initiated

Conclusions

- Although the first ATMP was approved 8 years ago, the PRMA landscape is still forming and evolving
  - Three of the eight approved therapies have been withdrawn; although it could be argued that these treatments were launched in areas where other therapeutic options were available
- All EMA approved ATMPs to date have faced EU5 access challenges, with Germany being particularly complex
  - HTA assessments have been unfavourable largely due to the uncertainty with available data and – possibly – costs
- There is a contradiction in terms of incentives that exist on the regulatory side for faster development of ATMPs (e.g. 6 ATMPs under PRIME program) versus the stark market access challenges with payers reluctance to reimburse these therapies
- Reimbursement paths need to solidify for AMTPs to be viable for the companies seeking to market them and the patients who will benefit
- Given the increased pace in submissions of new ATMPs, new models may be needed to address P&R issues especially for therapies that address a true unmet need
  - Strimvelis may be the first example of an ATMP following the path of innovative P&R mechanism already tried in other areas like oncology/orphan but with the uniqueness of having one ex-factory price set across the EU and a payment by instalment model negotiated at least with Italian authorities