BY ANY GENES NECESSARY: AN EVENTFUL 12 MONTHS IN THE GENE THERAPY PIPELINE

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INTRODUCTION

- It is without doubt an exciting time for gene therapies, with significant investment in recent years, and an increasing number of gene therapies reaching the market
- Despite the challenges faced commercially by some of the first gene therapies including Glybera and Strimvelis, Zolgensma is demonstrating the potential of high-cost, one-time treatments
- The broad reimbursement achieved for Zolgensma, including in countries such as Russia and Poland, and through initiatives such as Beneluxa demonstrates what is possible for gene therapy with advanced planning
- However, sobering reports have emerged from some payers, concerned about the potential budgetary impact of a wave of high-cost, one-time therapies reaching the market[1]
- With the FDA predicting 10-20 cell & gene therapy approvals per year by 2025[2], and a similar amount expected in Europe, there is a need to take a step back and consider the likely impact this may have on healthcare budgets

OBJECTIVE

- The objective of this poster is to review gene therapy pipeline developments in the previous 12 months, and draw out key themes emerging, considering implication for pricing & reimbursement

METHODS

- Cogentia analysed 100 gene therapies currently in clinical development, exploring developments & newsflow in the past 12 months
- Publicly available sources were analysed, including clinicaltrials.gov, and grey literature to establish developments in the previous 12 months
- Each gene therapy was then categorised as follows:
  - Positive development
  - Limited/no development
  - Negative development
- Qualitative mixed methods were used to draw out key themes emerging, considering both the manufacturer and the payer perspective
- The definition of gene therapy was limited to in-vivo or ex-vivo insertion of a gene, and did not include cell therapies, or gene editing therapies

RESULTS

Results of the analysis are presented in Table 2. Some of the key emerging themes in the gene therapy pipeline are described below:

- The challenge of ultra-rare disease
  - **Case study:** Orchard Therapeutics: three days after publication of 100% OS data for OTL-101 in the treatment of ADA-SCID in NEJM, Orchard Therapeutics abandoned OTL-101 amidst a reprioritisation effort, and a wider move from ultra-rare diseases to rare and prevalent disease[3-4]
- Cost of comparators & implications for P&R
  - **Case study:** Zolgensma: whilst the efficacy data for Zolgensma is incredibly compelling, Spinraza provided a significant price anchor, priced at €250,000 to €500,000 per year in spinal muscular atrophy. As previously described, Zolgensma has achieved a truly global footprint, this being one contributing factor.
- Rapidly evolving treatment landscape & moving to diseases with already effective treatments
  - **Case study:** wet AMD: enrolment for ocular gene therapy trials was already challenging after Adverum's SUSAR. Recent positive trial results for a 16-week dose of Eylea may make it even more challenging to recruit patients for clinical trials in wet AMD, as well as to compete assuming regulatory approval.

Table 1 Analysis of 5 near-term gene therapies using a framework to predict pricing & reimbursement success

Product	Disease area	Prevalence	Age in clinical trials (years)	Disease burden	Direct treatment costs	Current treatment options	Cost of comparator/year*	Successful analogue
Upstaza	AADC deficiency	<1/1,000,000	2+	Severe disability from the first months of life, typically fatal within 7 years in the severest form	Limited information, but studies report 50-100 HCP visits per year. 24/7 care	BSC, includes dopamine agonists, anticholinergics	Mostly low-cost generics	No analogues in Europe
Roctavian	Haemophilia A	5/100,000	18+	Life expectancy around normal with extensive treatments	BioMarin put the cost of lifetime treatment at $25m (US costs)	Factor VIII, Hemlibra	€400k-600k	Hemlibra has achieved broad reimbursement in Europe
SRP-9001	Duchenne Muscular Dystrophy	5/100,000	4-7	Rapidly progressive, lethal neuromuscular disorder.. Life expectancy <30 years	Ranging from €20k-50k per year as disease progresses	Corticosteroids, Translarna	€150k-300k, some patients only	Translarna has achieved mixed results in Europe,
Lumevoq	LHON	2/100,000	15+	Sudden loss of vision within 12 months of onset, typical onset 15-35 years	£5k-20k, driven by secondary care costs	Low vision aids, Raxone	Up to €75k for a small no. of patients	No analogues in Europe
Vyjuvek	Dystrophic epidermolysis bullosa	1-9/1,000,000	6 months+	Severe blistering, wounds, scarring. Increased risk of serious complications	$200k-400k/yr (estimates limited to US)	BSC, up to 4 hours/day skincare	Limited	No analogues in Europe

Ratings relate to impact on likelihood of positive P&R and commercialisation. Ratings span dark green (highly favourable) to orange (likely to prove challenging). As an example, a treatment for a disease with a reasonable prevalence,, early treatment with potential to accrue a lifetime of benefits, high disease burden, large cost offsets in resource use & comparator, and a successful analogue is well set for success. AADC, Aromatic L-Amino Acid Decarboxylase; BSC, best supportive care; HCP, healthcare professional; LHON, Leber's hereditary optic neuropathy.

Table 2 Number of investigational drugs that fit into each category

Pipeline developments in past 12 months	Number (n=100)
Positive development	27
Limited/no development	51
Negative development	22

- Whilst 50% of gene therapies have reported limited developments, 7/16 gene therapies at Phase 3 produced positive developments, potentially owing to the reduced risk as molecules progress through the clinic

DISCUSSION

- Our analysis provides an in-depth review of gene therapy developments, to better contextualise the excitement growing around gene therapy as a modality, as well as an assessment of the implications for market access
- Whilst the categorisation of gene therapies was based on subjective interpretation of their development in the previous 12 months, this was supported by definitions to support allocation, and allocation by two independent reviewers

CONCLUSIONS

- There have been significant developments in the gene therapy pipeline in the previous 12 months. By analysing the newsflow & clinicaltrials.gov, this poster presents a mixed picture, with roughly as many positive as negative updates
- Negative updates included 10 projects that were discontinued not due to their clinical profile, but instead due to re-prioritisation of funding, in often ultra-rare disease where companies state a move towards 'more prevalent' diseases.
- The challenge of ultra-orphan disease is a key emerging theme. We note the Beneluxa appraisal of Libmeldy as a gold-standard case study for supporting ultra-rare P&R, where single country submissions may be commercially unviable
- It is our view that beyond the clinical profile, challenges faced by gene therapies can often be anticipated with prior planning, and an early market access strategy is critical to avoid withdrawal, either in late-stage trials or after reaching the market
- Whilst things are certainly moving in the right direction for gene therapy, our findings suggest that the anticipated wave of approvals may instead be moving towards a more manageable flow

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