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

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BACKGROUND/INTRODUCTION

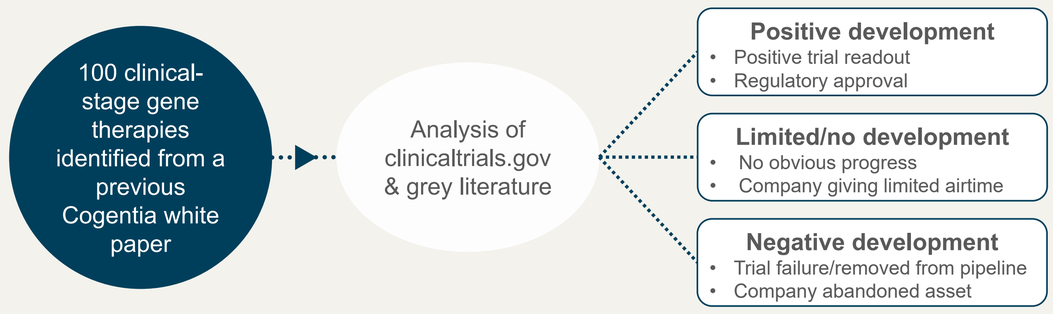
- It is without doubt an exciting time for gene therapies, with significant investment in recent years, and an increasing number of gene therapies reaching the market
- Despite the challenges faced commercially by some of the first gene therapies including Glybera and Strimvelis, Zolgensma is demonstrating 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 market1
- With the FDA predicting 10-20 cell & gene therapy approvals per year by 20252, 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(S)

- 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:** Upstaza: Listed at £3m a dose, reimbursement decisions are complex and time consuming as payers seek to minimise budget impact. In Italy, Upstaza used an early access programme called the "5% fund“ to provide access on a named-patient basis to orphan drugs whilst reimbursement decisions are pending[3]
- Struggle for uptake after launch
  - **Case study:** Roctavian: Despite being approved for use in the EU in August 2022, Roctavian took an additional 12 months to reach a commercial agreement and treat the first patient in Germany. Factors contributing to this delay include: the negotiation of complex commercial agreements based on patient outcomes and the struggle to establish screening protocols for the presence of pre-existing AAV5 antibody levels that would prohibit treatment with the gene therapy[4]
- Pressures of a competitive landscape
  - **Case study:** FLT180a: Freeline discontinued investment in November 2022 after questions regarding durability and the competitor landscape in haemophilia B[5]

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 per 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 neuro muscular 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,
Lovo-cell	Sickle Cell Disease	1/2000	12-50	Life expectancy shorter than normal. Chronic lifelong condition	Annual healthcare costs range from $15k - $30k	HC/HU. Crizanlizumab/ voxeletor.	~€70k	Crizanlizumab & voxeletor
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	33
Limited/no development	28
Negative development	39

- Whilst 28% of gene therapies have reported limited developments, 7/14 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 14 projects that were discontinued not due to their clinical profile, but instead due to re-prioritisation of funding, often following acquisitions by big pharma as commercial opportunities are re-assessed.
- The challenge of an increasingly competitive gene therapy pipeline is a key emerging trend. There is considerable competition in the haemophilia space with 20 gene therapies in clinical development for haemophilia B. For some such as Freeline Therapeutics, this competitive pressure has led to the discontinuation of gene therapy assets (FLT180a)[5] .
- 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

1. https://payorsolutions.cvshealth.com/insights/gene-therapy-keeping-costs-from-negating-its-unprecedented-potential
2. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics
3. Italy Reimburses Upstaza Via the 5% Fund for Rare Diseases | NAVLIN DAILY
4. Gene Therapies Are Still Hampered By Substantial Delays Between Approval And Launch (forbes.com)
5. Freeline puts the brakes on haemophilia B | Evaluate

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