COGENTIACAM™: POINTING THE LENS AT GENE THERAPY

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BACKGROUND/INTRODUCTION

- There has been a marked increase in late-stage developments in the gene therapy pipeline in the last year. In the period between mid-2022 and mid-2023 there were three gene therapies approved in Europe, and several others nearing regulatory decisions.
- 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 demonstrating 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]

OBJECTIVE(S)

- With the number of gene therapy approvals increasing, often with expectations of a single high-cost administration, there is a clear need to assess how to align payer and manufacturer perspectives. The objective was therefore to explore the potential of the gene therapy pipeline from a manufacturer perspective.

RESULTS

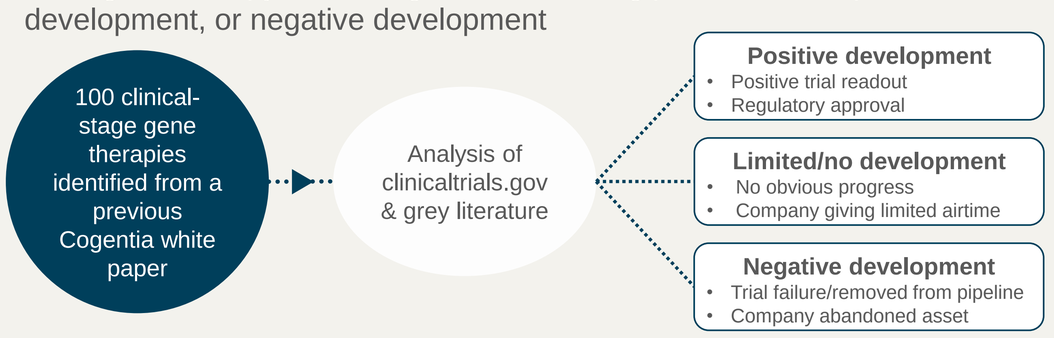
- Whilst 33% of all analysed gene therapies reported positive developments, 50% (7/14) of gene therapies at Phase 3 produced positive developments, potentially owing to the reduced risk as molecules progress through the clinic.
- Application of the CogentiaCAM™ tool suggested that the challenges for near term gene therapies were likely to vary.

Other key insights included:

- 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[2]
- 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 complex negotiation of commercial agreements based on patient outcomes and issues implementing required screening[3]
- 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[4]

METHODS

- In order to explore key themes emerging, Cogentia analysed 100 gene therapies in development or approved between mid-2022 and mid-2023, exploring public developments & news flow.
- Each gene therapy was categorised as having positive development, limited/no development, or negative development



- Subsequently, the potential of 5 near-term products was assessed using the Cogentia Commercial Attractiveness Matrix (CogentiaCAM™) to assess their potential.
- This matrix used qualitative mixed methods to draw out key themes, considering manufacturer and payer perspectives.
- 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

Table 1 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

DISCUSSION

- An in-depth analysis of 5 near-term gene therapy using the CogentiaCAM™ assessed the commercial potential, highlighting heterogeneity in the scoring across the tool domains.
- Qualitative analysis saw some key themes emerging, including:
  - issues with agreeing a sufficient evidence package in ultra-orphan conditions,
  - concerns around durability of effect,
  - the balance of benefit:risk and implications for evidence sufficiency,
  - and challenges achieving reimbursement and uptake for recently launched gene therapies

Table 2 CogentiaCAM™ framework applied to 5 near-term gene therapies 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.

CONCLUSIONS

- Examining the trajectory of recently approved gene therapies helps to demonstrate the challenges that treatments with a high-cost upfront and promise of benefits over the long term can face.
- There have been as many positive as negative updates, but the negative updates include 14 products discontinued due to re-prioritisation of funding, often following acquisitions.
- Where multiple gene therapies are targeting ultra-orphan conditions, there is likely to be a winner takes all outcome for the first entrant.
- To avoid further negative situations, it is important for manufacturers to understand the profile of their product from an early stage, both from a payer and partner perspective.
- 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.

RECOMMENDATIONS FOR MANUFACTURERS

Assess the market early

- Consider market landscape and competitive tracking from an early stage

Be clear on price and value

- Alongside landscaping, conduct elements of forecast modelling and early economic modelling, particularly for companies planning a European launch

Seek early input

- Conduct primary research with both clinical and payer profiles to understand tensions between perspectives

1. https://payorsolutions.cvshealth.com/insights/gene-therapy-keeping-costs-from-negating-its-unprecedented-potential
2. Italy Reimburses Upstaza Via the 5% Fund for Rare Diseases | NAVLIN DAILY
3. Gene Therapies Are Still Hampered By Substantial Delays Between Approval And Launch (forbes.com)
4. Freeline puts the brakes on haemophilia B | Evaluate