Kineticos Case Study

R&D Strategy

Kineticos conducted an indication prioritization analysis to help a pharmaceutical company identify specific diseases that coul be addressed with their novel platform technology and that also represented commercial viability

Situation:

A publicly traded biopharmaceutical company with a novel technology platform approached Kineticos about supporting their R&D strategy. The organization recently licensed one of their lead development programs to a top 10 pharmaceutical company and was in need of replenishing their pipeline. Because their platform was broadly applicable across indications, there was a need to conduct an objective indication prioritization exercise.

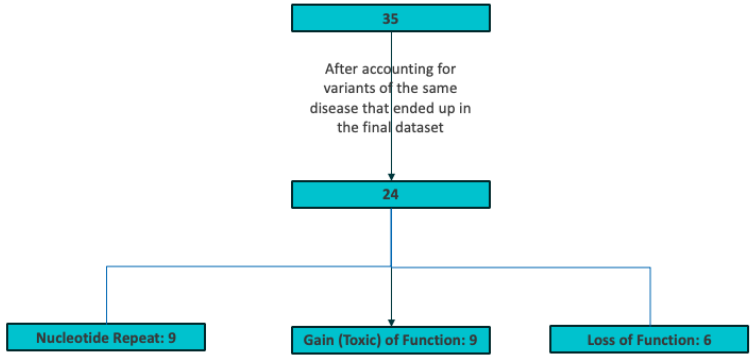
Process:

With the sponsor having a focus in rare diseases, Kineticos was ultimately charged with narrowing a list of over 9,400 rare diseases to the 5 most attractive indications from a technical and commercial perspective. Kineticos first worked with the client to develop baseline criteria for the target diseases and subsequently combed through proprietary databases to remove diseases that did not meet the initial requirements from consideration. The output of this exhaustive and methodical screening process included a list of 35 diseases that were then scored and weighted based on various criteria established collectively between Kineticos and the sponsor. Once rank ordered, Kineticos conducted a sensitivity analysis to identify other diseases that could potentially disrupt the original top 5. Upon receiving approval on the top 5 diseases, Kineticos conducted a detailed review of each disease. This review included assessing the disease state, current standard of care, competitive landscape, unmet medical needs, timing to market, probability of success, and commercial potential. The detailed assessments resulted in the sponsor selecting 2 indications for final consideration. The final step included conducting Key Opinion Leader interviews with leading researchers to validate secondary findings and to fill any remaining information gaps regarding the 2 diseases and the viability of their technology treating the underlying diseases.

Outcome:

Kineticos equipped the sponsor with a database of over 9,400 diseases with an objective ranking of the top 35 diseases. The database was built in such a way that it was clear which specific filters resulted in specific diseases being removed from consideration as well how the top 35 were scored, weighted, and ranked. Also provided to the client was a PowerPoint deck that provided a detailed methodology outlining the filtering/scoring process, an assessment of the top 5 diseases, key themes and insights gained through the KOL interviews and recommendations on potential follow on indications.

Inclusion/Exclusion Methodology
Draft List of Diseases by Type



Proposed Weighting/Index Generation

We propose using the following weights:

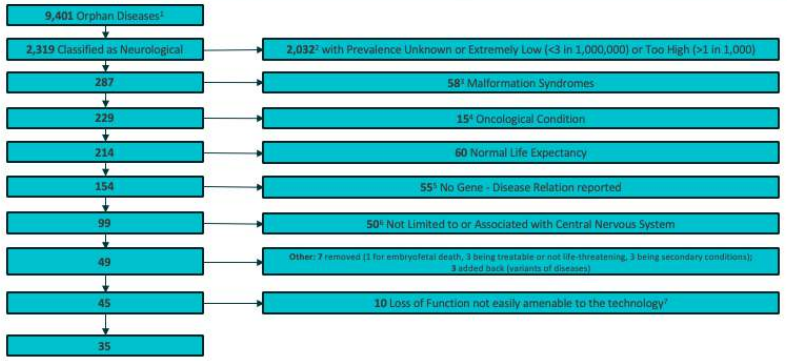
Medical	Weight		Notes
Unmet Medical Need	40%	30%	The key metric - a proxy for potential medical impact and pricing / market access. Criteria to be developed, may be partially subjective
Diagnosis Rate		10%	To understand if there are diseases with higher prevalence, but in which patients are not easily diagnosed

Strategic	Weight		Notes
Portfolio Fit	30%	10%	Input requested from CLIENT team on potential portfolio/company level metrics not currently under consideration
Probability of Success		20%	Input requested from CLIENT team on assessment of POS (technical & regulatory) for each project

Commercial	Weight		Notes
Time to Launch	30%	10%	Based on likely clinical program for each project, using prior or current trials from other companies and regulatory guidance
# of Patients		20%	Based on prevalence figures

Unmet Medical Need (30%) X # of Patients (20%) X Diagnosis Rate (10%) X Time to Launch (10%) = **[Proxy for] Financial Opportunity (70%)** X Probability of Success (20%) = **[Proxy for] Risk-Adjusted Financial Opportunity (90%)**

Inclusion/Exclusion Methodology



1 In proprietary database compiled from several sources on Orphanet; counts each variant or sub-type as separate disease
2 Of these, 45 were manually excluded; they showed up in the prevalence = 1-9 in 1,000,000 group, but in fact had a figure of <1 in 1,000,000, or because their diagnosis is extremely low
3 Of these, 8 were manually excluded; they were listed as Diseases and not Malformation Syndromes but hallmark features cannot be corrected after birth (e.g. holoprosencephaly)
4 Of these, 7 were manually excluded (e.g. multiple myeloma)
5 Upon review, there are infectious diseases (e.g., Botulism, Tetanus, Rabies, Encephalitis, Lyme, Meningitis), oncological conditions not previously eliminated; 1 was manually excluded
6 These were manually excluded after thorough review; conditions may be multi-system (e.g. some Lysosomal Storage Diseases), primarily affecting another system (e.g. lupus, sickle cell anemia, muscular dystrophies) or affecting the peripheral nervous system (e.g. Charcot-Marie-Tooth)
7 For example, too many SNPs or mechanism of action of gene not well understood to look at complementary gene silencing

Preliminary Scoring

Disease	Gene	Total Score	Unmet Medical Need	Time to Primary Endpoint	Probability of Success	# of Competitors	# of Patients
INDICATION #1	torsin A (TOR1A / DYT1)	12	2	3	3	3	1
INDICATION #2	Huntingtin (HTT)	11	2	3	2	1	3
INDICATION #3	Ataxin 3 (ATXN3)	11	2	3	2	2	2
INDICATION #4	proteolipid protein 1 (PLP1)	11	3	3	2	2	1
INDICATION #5	arylsulfatase A (ARSA)	11	3	3	2	2	1
INDICATION #6	Ataxin 1 (ATXN1)	10	2	3	2	2	1
INDICATION #7	Ataxin 7 (ATXN7)	10	2	3	2	2	1
INDICATION #8	MAP tau (MAPT)	10	1	3	3	1	2
INDICATION #9	MAP tau (MAPT)	10	1	3	3	1	2
INDICATION #10	Glutaryl-CoA dehydrogenase	10	3	2	2	3	0
INDICATION #11	MT-ATP6	10	3	2	2	3	0
INDICATION #12	laforin glucan phosphatase (EPM2A)	10	3	3	2	2	0
INDICATION #13	Frataxin (FXN)	9	2	3	2	1	1
INDICATION #14	C9ORF72	9	1	3	2	2	1
INDICATION #15	C9ORF72	9	1	3	2	2	1
INDICATION #16	Notch 3	9	1	2	2	3	1
INDICATION #17	4 genes involved	9	3	2	2	2	0
INDICATION #18	galactosylceramidase (GALC)	9	3	2	2	2	0
INDICATION #19	SMN1/2	9	3	3	2	0	1
INDICATION #20	AF4/FMR2 family member 2 (AFF2)	8	1	1	2	3	1
INDICATION #21	Transthyretin (TTR)	8	1	3	3	0	1
INDICATION #22	PSEN1/2	8	2	3	1	0	2
INDICATION #23	Ataxin 2 (ATXN2)	7	1	2	2	2	0
INDICATION #24	a-Synuclein (SNCA)	7	2	2	1	0	2
INDICATION #25	a-Synuclein (SNCA)	7	1	1	1	2	2

Diseases of Interest | Good understanding already
Part of Existing Collaboration | Eliminated for Other Reasons

INDICATION #1

	0	1	2	3
Probability of Success	0%	Less than 50/50; loss of function that may have multiple compensatory mechanisms, such that the technology may not fully address condition.	About 50/50; loss of function that can likely be fully compensated by knockout of a single gene.	Better than 50/50; single gene or mutation to address; gain of function that appears easily amenable to the technology.

Rationale

Dyt1 homozygous knockout (KO), *Dyt1 p.Glu303del* homozygous KI, and KO/KI double mutant mice resulted in neonatal

- **Whether it is due to a dominant loss of function / haploinsufficiency or a toxic gain of function due to aggregation and formation of perinuclear inclusion bodies is still of contention.**

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INDICATION #1

	0	1	2	3
Time to Primary Endpoint	> 8 years; or primary endpoint impossible to measure or unknown.	5 to 7 years; requires development of an animal model or difficult model for POC; clinical trial expected to be long to see clinical benefit / endpoint.	3 to 4 years; animal model readily available; clinical trial should allow POC relatively quickly, but there may be difficulties in recruitment.	1 to 2 years; animal model readily available; therapy should result in very quick readout and patient population should be easy to recruit.

Rationale

Primary Endpoint:

- a reduction in the Burke-Fahn Marsden Dystonia Rating Scale (BFMDRS); patients are videotaped and scored by blinded reviewers; rate the severity of

Pre-Clinical Models:

- Multiple *Drosophila* and *C. elegans* models
- Human and rodent genes are highly homologous.
- Multiple DYT1 genotypic dystonia models have been

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INDICATION #1

	0	1	2	3
Epidemiology	< 1,000 in US 3 in 1 million	1,000 to 10,000 in US Up to 3 in 100,000	10,000 to 100,000 in US Up to 3 in 10,000	> 100,000 in US > 3 in 10,000

Rationale

- 1:3000 to 1:9000 in Ashkenazi Jews (carrier frequency due to penetrance estimated at 1:1000 -1:3000)
- 1:10,000 to 1:30,000 in non-Jews
- The DYT1 mutation is responsible for about 90% of INDICATION #1 in individuals of Ashkenazi Jewish ancestry and up to about 50% of INDICATION #1 in other ethnicities.

	0	1	2	3
Competition	Very High (relative to orphan condition); > 5 pipeline assets in clinical development.	High (relative to orphan condition); 3 to 5 pipeline assets in clinical development + an equal amount in preclinical development.	Low (relative to orphan condition); 1 to 2 pipeline assets in clinical development + an equal amount in preclinical development.	None (relative to orphan condition); NO pipeline assets found in preclinical or clinical development.

Rationale

- Have only found a group at CHOP that is working on a similar solution

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INDICATION #1

	0	1	2	3
Unmet Medical Need	No impact on life expectancy. No negative impact on QoL or symptomatic condition well managed by many treatments that are readily available.	Some impact to life expectancy (>55 years but less than normal) or some negative impact on QoL even after therapeutics.	High impact to life expectancy (>18 years but less than 55) or high negative impact on QoL, perhaps due to lack of therapeutics or even with therapeutics.	Very high impact to life expectancy (<18 years) or very high negative impact on QoL. No treatment of any kind available.

Rationale

Current Therapeutics before DBS:

- Oral anticholinergics (particularly trihexyphenidyl), baclofen, ± benzodiazepines (particularly clonazepam)
- Botulinum toxin injection for focal symptoms
- Aggressive surgical intervention to prevent joint contractures & spine deformities

- No impact to life expectancy for most patients
- Onset during adolescence makes it a life-long condition with variability impact to QoL
- More severe symptoms include pain and exhaustion due to constant muscle contractions
- 75% of patients maintain ambulation and independence, with modern treatment modalities
- **For 25% with severe, medically refractory dystonia,** only deep-brain stimulation (DBS) of the globus pallidus interna (GPi) is a treatment option; most DBS patients undergo repeat surgeries to replace the implantable pulse generator every 2.5 to 5 years.
- Long-term orthopedic complications may include joint contractures or spine deformities

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