LEVERAGE - UTILISING EARLY ECONOMIC MODELLING TO MAXIMISE PRODUCT VALUE, AND EVIDENCE DEVELOPMENT, BY QUANTIFYING VALUE LEVERS.

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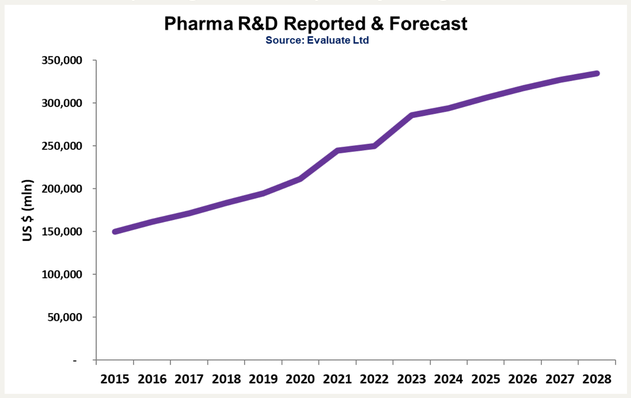
BACKGROUND

- The cost and investment in R&D is increasing from an already high level, and therefore ensuring sufficient return on investment (ROI) is ever more important at the outset.
- Identifying what to target, outcomes to be achieved, and evidence requirements to maximise the value of the asset is required early. The process by which Target Product Profiles (TPPs) can be optimised and maximised is nuanced and iterative, requiring multidisciplinary insights and collaboration.
- Early economic modelling (EEM) is a mechanism and a process by which this can be facilitated and assists in communicating the potential value of the TPP (under different scenarios), but also in deliberating on potential thresholds and trade-offs.
- Inclusion of EEM at the start of clinical development is a timely and efficient intervention. We present a case study to demonstrate how health economic modelling, integrated with a forecast model, can enhance the robustness and value of an early-stage asset.



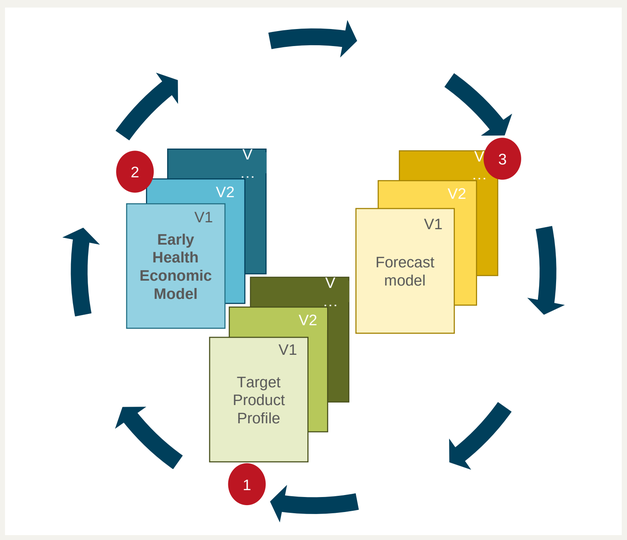
- Health economics is intrinsically interlinked with net present value (NPV):
  - The clinical outcomes achievable can differ between patient subgroups, which underpins cost effectiveness, the pricing corridor and the size of the target patient population
  - The price, patient numbers, clinical trial size and economic evidence generation activities are key drivers of net present value (NPV).

OBJECTIVE

- Demonstrate how early health economic modelling can optimise strategic development using a case study of a hypothetical acute care product

APPROACH

1. Following a landscape assessment, a range of potential target product profiles are developed .
2. Use the early economic model – to explore the value, potential pricing and key uncertainties, stopping rules, sub-populations or potential evidence gaps, around that TPP.
3. Then to use a linked forecast model , to explore what the impact of such a decision / TPP is with regards budget and returns on investment or revenues. Considering the trade-offs between price, volume, or even later launches with longer clinical development, and factoring in risk



CASE STUDY

- Drug X is a pre-phase III hypothetical acute care product used for the treatment of aneurysmal subarachnoid haemorrhage (aSaH), a rare but serious type of spontaneous neurovascular injury
- Two separate but interacting Excel models were developed to evaluate the cost effectiveness and risk-adjusted NPV of drug X in aSaH patients with a World Federation of Neurological Societies (WFNS) status of 2 to 4 at admission (lower score indicating better neurological status)

Economic model

	Total costs	QALYs	Incr costs	Incr QALYs	ICER
Drug X	€ 233,186	2.449	€ 12,311	0.410	€ 30,000
Standard of care	€ 220,874	2.038			

Population
WFNS status: WFNS3 only (WFNS 2-4 / WFNS 2-3 / WFNS 3-4 / WFNS2 only / WFNS3 only / WFNS4 only)
Proportion WFNS2 (value overrides trial data)
Proportion WFNS3 (value overrides trial data)
Proportion WFNS4 (value overrides trial data)
Patient age

Discount rates
Costs discount rate 3.50%
Outcomes discount rate 3.50%

Treatment options
Cost of Drug X € 19,426

QALY gain

	WFNS 2	WFNS 3	WFNS 4
Base	0.121	0.410	0.379
Worst	0.077	0.325	0.288

Price

	WFNS 2	WFNS 3	WFNS 4
Base	€ 6,640	€ 19,426	€ 28,758
Worst	€ 3,320	€ 9,713	€ 14,379

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- An economic model was developed in Excel for drug X vs. the current in-hospital standard of care (SoC) protocol
- The model used modified Rankin scale (mRS) as the key clinical measure of neurological disability from which costs and quality adjusted life years (QALYs) were derived. Base case outcomes were informed by phase II data

1. As neurological status at admission is a key driver of neurological outcome, the model was structured to analyse outcomes by WFNS status at admission
2. Using the Excel 'Goal Seek' threshold analysis tool, the maximum price for drug X permitting an incremental cost effectiveness ratio (ICER) of €30,000 was tabulated for each subgroup, based on estimates of base vs. worst case efficacy (which could be calculated from Phase II studies).
3. QALY gain for each scenario was also tabulated, as QALY gain can be considered a proxy for absolute clinical benefit and likely uptake (market share) of the drug

- The model was also used to identify further real-world evidence (RWE) requirements, which were to be accounted for in the discounted cash flow model. As aSAH trials are generally of short duration, these largely comprised capturing the long-term costs and quality of life of patients according to their mRS score at 3 months

CONCLUSIONS

- **Early health economic modelling is a useful tool to guide early development decisions**
- **Value can be optimised at the outset – and a clearer understanding achieved through utilising early economic modelling, forecasting and TPP scenario planning**
- **This approach is likely to be cost effective and value enhancing for the majority of development and is recommended.**

RESULTS

9. Using the two models, a structured table of potential product profiles was produced with details of the price, patient population and size, efficacy assumption, potential patient share, development costs, ICER and NPV
   - Based on the table, and analysis – there was a clear value maximising scenario
   - Optimal ROI and least risky option was to develop drug X for WFNS 3 to 4 patients only, despite this being a subgroup. A worst-case scenario when developing for WFNS 2-3 could potentially lead to a non-profitable product

Forecast Model : Risk-adjusted Discounted Cash Flow (DCF)

- A DCF model was developed in Excel to evaluate the NPV of drug X over a 10-year time horizon, staring from initiation of phase III clinical studies
- Estimates of clinical development costs and success rates were obtained from the published literature (Mestre-Ferrandiz et al., 2012)

4. The DCF model was structured to analyse NPV by any combination of WFNS subgroup(s)
5. QALY gain in each WFNS subgroup informed relative scale of market penetration of drug X in that subgroup
6. Price of drug X for each WFNS subgroup was informed by the economic model threshold analyses. A 'blended price' was calculated based on the proportions of patients in each subgroup
7. Clinical development costs were based on reported recruitment numbers in a published phase III trial protocol, but were weighted based on the potential QALY gain in each subgroup (Clinical Trials.gov, 2016)
8. RWE studies to support HTA and market access activities were informed by the evidence gaps in the economic model and costed for the DCF model

EUROPE

			2019	2020	2021	2022
Incidence (per 100,000)	0.00006					
Population EU 28 (1000s)	512,379					
Subarachnoid haemorrhage patients	0.5%	CAGR	31,255	31,411	31,568	31,720
WFNS grade 2 ☑	25.3%	Proportion	7,908	7,947	7,987	8,027
WFNS grade 3 ☑	7.2%	Proportion	2,250	2,262	2,273	2,284
WFNS grade 4 ☑	10.9%	Proportion	3,407	3,424	3,441	3,458

Treated patients

Market penetration WFNS grade 2 base efficacy	12.1%		0%	0%	0%	1%
Market penetration grade 2 worst efficacy	50.0%	Relative %	0%	0%	0%	1%
Market penetration WFNS grade 3 base efficacy	41.0%		0%	0%	0%	5%
Market penetration grade 3 worst efficacy	50.0%	Relative %	0%	0%	0%	3%
Market penetration WFNS grade 4 base efficacy	37.9%		0%	0%	0%	5%
Market penetration grade 4 worst efficacy	50.0%	Relative %	0%	0%	0%	2%
Total patients	Worst	Efficacy	0	0	0	196

Price (Euros) — **Revenues using blended price** (E

Drug X price WFNS 2 base efficacy	6,640	Price	0	0	0	848
Drug X price WFNS 2 worst efficacy	3,320	Price	0	0	0	424
Drug X price WFNS 3 base efficacy	19,426	Price	0	0	0	818
Drug X price WFNS 3 worst efficacy	9,713	Price	0	0	0	409
Drug X price WFNS 4 base efficacy	28,758	Price	0	0	0	1,144
Drug X price WFNS 4 worst efficacy	14,379	Price	0	0	0	572

Total revenues using blended price (Euros 1000s

Blended price	7,158		0	0	0	1,405

Clinical development (Euros 1000s)

Per patient cost (Euros)	40,000					
Develop for WFNS grades 2-4	400	Patients	3,200	3,200	0	0
Develop for grades WFNS grades 2-3 only	600	Patients	4,800	4,800	0	0
Develop for grades WFNS grades 3-4 only	300	Patients	2,400	2,400	0	0

RWE generation (Euros 1000s)

Cost of SaH patients by mRS score	250	Study cost	0	0	250	0
Utility of SaH patients by mRS score	500	Study cost	0	0	500	0

Regulatory and Market Access (Euros 1000s)

Regulatory	3,000	Study cost	0	600	2,100	300
Market access	4,000	Study cost	0	0	1,000	2,000

P&L (Euros 1000s)

Revenue			0	0	0	5,619
Cost of goods sold drug X (Euros 1000s)	2,000		0	0	0	785
Gross profit			0	0	0	4,834
Clinical development and RWE			3,200	3,800	3,100	2,300
Regulatory/HTA filings			0	600	2,100	300
Sales & marketing	20%	% sales	0	0	0	1,124
General & administrative	5%	% sales	0	0	0	281
Risk-adjustment			100%	100%	70%	64%
EBITDA			-3,200	-4,400	-3,640	1,207
Depreciation and amortisation						
Interest and tax	20%		0	0	0	241
NPAT			-3,200	-4,400	-3,640	966
Change in working capital			0	0	0	923
Free cash flow			-3,200	-4,400	-3,640	1,889
Discounted cash flow	11.5%		-3,200	80	-2,928	1,363
Net present value			7,122			

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NPV summary (Euros 1000s)

	Base NPV	Worst NPV	Best price	Worst price	Best peak patients	Worst peak
WFNS 2-4	51,031	7,122	14,316	7,158	3,349	1,675
WFNS 2-3	13,881	-3,418	9,473	4,736	1,985	993
WFNS 3-4	64,761	11,177	25,045	12,523	2,339	1,169

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