Evaluating Market Value of a Biologic Therapeutic to Treat Dercum's Disease Based on Risk-Adjusted Net Present Value and Monte-Carlo Simulation

Murali Vemula, PhD[1]

[1]Nivarta Inc., 1 Kendall Square, Cambridge, MA 02139

The worldwide orphan drug sales are expected to reach $178 billion by 2020. This has made rare diseases an important sector to be considered for financing by private and public sectors. In the last decade, sufficient data has become available based on marketed orphan drugs to build financial models and forecast revenues. Despite this, very few valuation models are available in the public domain to give a perspective on the revenues and costs associated with developing and marketing new rare disease products. Broadly speaking, the development of an orphan drug is not that much different from developing any other pharmaceutical product except that the target patient population is much smaller. The small number of potential users, however, brings in new challenges in terms of production, marketing, distribution and reimbursement potential. Here, we attempt to provide a risk-adjusted Net Present Value model to estimate the market value of developing a therapeutic to treat a rare disease, Dercum's Disease. Such a model will hopefully provide some guidelines that can be used by originators, investors, and acquirers to make judicial investment decisions.

INTRODUCTION

Dercum's Disease

Dercum's Disease (DD) affects less than 200,000 patients in the United States and is characterized by presence of multiple painful fat deposits with or without nodules (likened to lipomas) just under the skin (Wortham and Tomlinson 2005, Herbst 2012). The fat depots/nodules can vary in size – some as small as a pea to as large as a football or even bigger. A significant amount of pain is associated with these fat depots, to the extent that pain killers such as lidocaine is commonly prescribed (Devillers and Oranje 1999). Currently, there is no FDA approved drug to treat the disease. The standard procedure is to surgically remove the fat deposits. In many patients, a spread in inflammation resulting from surgery leads to formation of additional fat depots/nodules. Moreover, recurrence of fat depots at the site of surgery is common. Each instance of surgery requires hospital stay for several days as this is an invasive procedure. The development of a non-surgical alternative, such as a therapeutic drug, to reduce the size or eliminate the fat depots will reduce the burden of hospitalization and greatly improve the quality of life in these patients.

Risk-Adjusted Net Present Value Model (rNPV)

The discounted cash flow (DCF) method takes free cash flows generated in the future by a specific project/company and discounts them to derive a present value (i.e. today's value). The risk adjusted net present value (rNPV) method employs the same principle as the DCF method, except that each future cash flow is

risk adjusted to the probability of clinical success. Introducing clinical-trial success rates as a pay-off probability incorporates the main risk driver, which enhances the valuation (Stewart, Allison et al. 2001, DiMasi, Feldman et al. 2010, Svennebring and Wikberg 2013). Moreover, the incorporation of clinical-trial success rates into more traditional DCF analyses is useful to price the current values of biotech projects as they are being developed. For this reason, rNPV has become the *de facto* method to value compounds or products in the pharmaceutical and biotech industry. To calculate rNPV, four general parameters must be known: projected market (sales), costs, orphan drug status, clinical success rates and discount rate.

The following model evaluates the value of developing a biologic therapeutic to treat a rare indication, Dercum's Disease. The model is based on risk-adjusted rNPV. The parameters that would affect the pre-clinical and clinical development have been used to estimate costs and project revenues. In addition, the costs to be incurred during phase 1, 2, and 3 of clinical development have been risk adjusted based on the success rates. Furthermore, the parameters have randomized based on triangular distributions and simulated using Monte-Carlo methods to identify the ones that most influence rNPV in this model. Such a model will hopefully provide some guidelines that can be used by originators, investors, and acquirers to make judicial investment decisions.

Parameter Assumptions

Revenue
Number of cases forecasted for Year 1: 25,000
Annual growth rate: 3%
Peak market penetration rate: 20%
Average cost/patient/year: $75,000
Market ramp time to peak: 3 years

Orphan drug tax credits: 50% of clinical trial costs returned as tax credits

Costs
Pre-clinical research: $20 million
Phase 1: $50,000 per subject
Phase 2: $100,000 per subject
Animal studies to support phase 1: ~$2.5 million
Animal studies to support phase 2: ~$5.0 million
Manufacturing/Marketing: 40% of revenue
FDA approval costs: ~$1.3 million
Annual patent costs/fees: $100,000

Discount rate (R&D risk considered separately): 25%
Tax rate: 25%

REVENUE FORECASTS

Customer Profile and Market Size

In the absence of an epidemiological study accounting for the exact number of patients suffering from DD, an informal survey was conducted by reaching out to several physicians who are treating patients with these indications (Herbst 2012). The general consensus is that there are less than 200,000 patients with DD. This estimate is based on the criteria that were most recently proposed to characterize DD(Hansson, Svensson et al. 2012). The subjects exhibit generalized over- weight or obesity with pronounced pain in the fat tissue. The pain is chronic (>3 months), symmetrical, often disabling and is resistant to traditional analgesics. The presence of small lumps in subcutaneous adipose tissue (SAT) is a requirement for diagnosis. The types of DD can be 1) Diffuse: Lipomas may be small, the size of a pea, and diffusely affect the majority of SAT. 2) Nodular: Lipomas are in the size of a marble, walnut, fist, or larger, localized primarily on the arms, anterior rib cage, abdomen, low back, buttocks and thighs or 3) Mixed: A combination of diffused and nodular lipomas. For the purposes of this model, a highly conservative number (25,000 subjects) has been used given that an accurate count is not available as yet.

Market Penetration Rate

The peak market penetration rate (20%) used here is higher than generally assumed rate (5%). This can be justified given that several hospitals and centers such as the one in University of Arizona are already attending to a large patient pool. In addition, the target disease is untreatable at this point as there is no FDA approved drug on the market. Hence, it will be possible to recruit additional subjects easily.

Pricing & Reimbursement

The standard of care treatment for Dercum’s Disease is surgical excision of localized fat depots combined with

Table 2. **Risk-Adjusted NPV (in $1000s)**

Year	Description	Risk-Adjusted Income/Loss	rNPV
1	Pre-clinical Development	(20,100)	(20,100)
2	Phase 1 human year 1	(2,201)	(1,760)
3	Phase 2 human year 1	(1,090)	(697)
4	Phase 2 human year 2	(1,090)	(558)
5	FDA approval	(266)	(109)
6	Sales Revenue (ramp-up)	48,907	16,025
7	Sales Revenue (ramp-up)	100,749	26,410
8	Sales Revenue (peak)	155,656	32,643
9	Sales Revenue (peak)	213,767	35,864
10	Sales Revenue (ramp-down)	220,180	29,552
11	Sales Revenue (ramp-down)	226,786	24,350
12	Sales Revenue (ramp-down)	233,589	20,065
13	Sales Revenue (ramp-down)	180,478	12,400
14	Sales Revenue (ramp-down)	123,908	6,811
15	Sales Revenue (ramp-down)	63,812	2,806
	Total		**183,705**

or without liposuction. Every instance of surgical excision roughly costs $100,000, which includes hospital stay and surgeon's compensation. Hence, a patient is likely to pay higher than $100,000 per treatment for a drug if it provides superior benefits to standard-of-care treatment. The upper limit on pricing will, however, largely depend on reimbursement policy through insurance companies and Medicare.

A large percentage of Medicaid state plans do not treat the coverage of orphan drugs differently from that of drugs for prevalent diseases. The States often have little or no basis on which to make cost-effectiveness decisions, because they are required to cover drugs for which they receive a rebate. The Medicaid Drug Rebate Program requires a drug manufacturer to provide a rebate of at least 13% of the drug's cost for it to be covered by a state Medicaid program. Therefore, any manufacturer that provides a rebate has a drug that Medicaid providers must cover, automatically putting the medication onto the state formulary list. This drug access and coverage policy is in turn pushed onto managed care organizations (MCOs), requiring the MCOs to cover any drug that a given state covers.

Like state Medicaid plans, several private insurers do not have resources for conducting cost-benefit or cost-effectiveness analyses, citing thin margins and insufficient budgets for studies. Consequently, payers often rely on what is published and on what is preferred by healthcare providers, together with assessments based on drug monographs, and, at times, input from external consulting firms and market intelligence.

Like all pharmaceuticals, orphan drugs have specific indications. Physicians are responsible for verifying the needs of patients with a rare disease and for correctly directing them to novel therapies for rare diseases. Then insurance companies screen the claims and can refuse payment unless the screening criteria are met. This critical element—evidence of substantiation—is the leverage point on which the decision is made. The FDA neither calls into question the cost nor the appropriate level of cost associated with a drug, only whether it is effective or better than nothing.

EvaluatePharma® estimates that the average cost per patient per year in 2017 for an orphan drug was $111,820 (Hadjivasiliou 2017). The sensitivity to drug cost ranges considerably amongst 26 surveyed plans that insure 61% of US population. For two plans, drug cost must exceed $250,000 per patient per year for

Table 3. **The list of parameters that were randomized based on triangular distribution in order to perform Monte-Carlo simulation**

Parameter	Low	Base	High
Number of Cases Forecast for Year 1	5,000	25,000	50,000
Peak Market Penetration Rate	10%	20%	30%
Average Cost/Patient/Year	$25,000	$75,000	$100,000
Pre-Clinical Costs	$10 million	$20 million	$30 million
Per Patient Phase 1	$25,000	$50,000	$75,000
Per Patient Phase 2	$50,000	$100,000	$150,000
Animal Studies (Phase 1)	$1.25 million	$2.5 million	$3.75 million
Animal Studies (Phase 2)	$2.5 million	$5.0 million	$7.5 million
Manufacturing/Marketing	30%	40%	60%
Discount Rate	20%	25%	40%

greater scrutiny. In about 30% plans, the cost is scrutinized when a drug is priced at $100,000 or greater.

In summary, as is typical with rare diseases drug development, price elasticity is reflected in the expected clinical benefit for the patient. Given that the product is presumed to be in preclinical stages, all pricing assumptions are dependent on establishing a clinical profile that meets or exceeds standard of care treatment.

Orphan Drug Tax Credits

The orphan drug tax credits (ODTC), 50% of clinical trial costs, that the company receives from the US government has been considered as revenue to the company although it is not generated through sales. This is because, in effect, money into the coffers of a company that can used at its discretion.

PROJECTED COSTS

The costs are based on the development of a peptide therapeutic that can be injected systemically or directly into the fat depots/nodules to reduce or completely eliminate the depot. In this scenario, multiple injections might be necessary depending the size and distribution of depots. The projections are based on the assumption that a lead has been identified and optimized for clinical applications.

Pre-clinical & Clinical

The costs include scale-up, manufacturing clinical grade biologic product under GLP guidelines, safety and toxicology assessment, and efficacy studies in rodents and another small animal model. An estimate of $20 million is rather high when compared to a small molecule drug. However, this is not atypical given the high costs associated with biologic manufacturing.

For any new molecular entity (NME, a novel chemical pharmaceutical or biologic) to be marketed in the U.S. that NME must gain approval from the Food and Drug Administration (FDA). FDA approval, in turn, hinges on clinical trials — a series of experiments performed on humans. These clinical trials are generally conducted in three phases. In phase I, 20-80 healthy volunteers are given the NME to determine if it is toxic in humans. If the NME has a safe dose, then 100-300 patients are given the NME in a phase II trial to see if it successfully treats the condition for which it is intended. If the NME appears to be effective then it is submitted to 1,000-5,000 patients in a phase III trial in which efficacy is confirmed and patients are monitored for long-term side effects. In case of orphan drug development, a much smaller number of patients are required. A phase I requires 20 volunteers and phase II requires 20-250 patients. Moreover, phase III is not required as the number of estimated patients with a rare disease is generally low. All three clinical trials also have concurrent direct costs for animal studies that test for toxicity, the propensity to cause birth defects, and the like. These animal studies are required by the FDA

to support clinical trials. The costs related to clinical studies have been priced at $50 thousand per patient in phase I trial and $100 thousand per patient in phase II (Orfali, Feldman et al. 2012).

Royalty rate

There are no royalties associated with the product being considered in this model. However, there is typically some form of royalty to be paid as the technology or initial product is in-licensed. Alternatively, there might be royalty to be received from a company that has acquired to sell the product.

Manufacturing & Marketing

A 40% of the projected revenues is reserved for the eventual marketing and manufacturing either by the company itself or a partner/acquirer.

CLINICAL SUCCESS RATES

There is a reasonably large body of data on the success rates of NMEs in clinical trials. Data are published periodically in summary form by the Tufts University Center for the Study of Drug Development (www.tufts.edu/med/csdd/). The probability of progressing from one development stage to the next, based on widely used benchmarks in the industry are: Phase 1 to phase 2 trials: 71%; Phase 2 to phase 3 trials: 45%; Phase 3 trials to pre-registration: 64%; and Pre-registration to product approval: 93%. In the rNPV model, the net cash flow is multiplied by the cumulative probabilities at each stage; i.e. all cash flows from phase 1 to phase 2 are multiplied by 0.71, from phase 2 to phase 3 by 0.71 x 0.45 = 0.32, etc.

COST OF CAPITAL

The cost of capital is based on the assumption that an equivalent to the 25% internal rate of return is generally expected by the primary sources of capital available to biotechnology companies—venture capitalists and large pharmaceuticals companies.

TIME PERIOD OF ANALYSIS

The current analysis starts at Year=1, which is the year of pre-clinical studies that includes manufacturing and production of clinical grade biologic in GLP facilities and conducting safety and efficacy evaluation in non-primate species. The phase I studies would occur in Year 2 and phase II studies in Years 3 & 4. The FDA approval is assumed to come through in Year 5. The revenues have been projected for the next ten years.

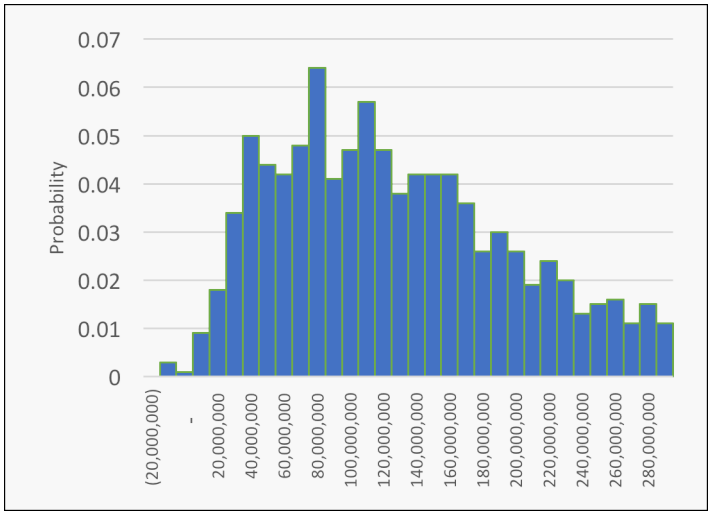

Figure 1: **Probability Distribution Plot of rNPV Following Monte-Carlo Simulation of Parameters**

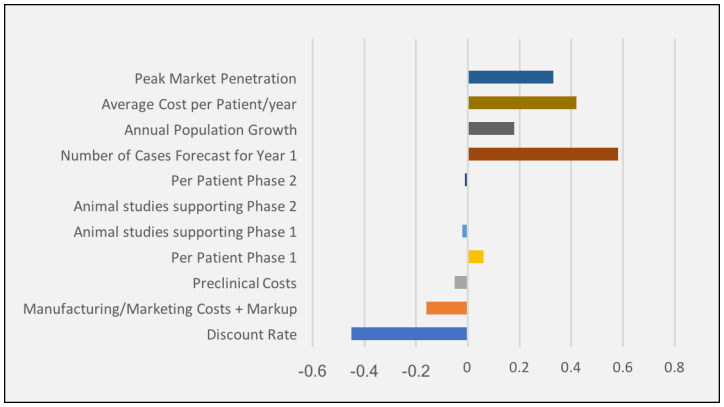

Figure 2: **Correlation with rNPV**

SENSITIVITY ANALYSIS

The parameters that influenced the rNPV most were identified using Monte-Carlo simulation method. Several parameters were randomized based on triangular distributions. The Low, Base, and High values were empirically set for each parameter based on published or public data (Table 3). rNPV was calculated for each of 1000 simulations. A probability distribution graph was drawn based on the frequency of occurrence (Figure 1).

The distribution showed a positive skew suggesting the possibility of frequent small losses and a few extreme gains. The rNPV showed a mean approximately $137 million, which is greater than median ($118 million) but within one standard deviation as observed in the base case scenario. A correlation analysis of parameters against rNPV showed that Number of Cases Identified, Average Cost per Patient, and Peak Market Penetration Rate increased rNPV while Discount Rate and Manufacturing/Marketing costs lowered rNPV.

DISCUSSION

The Orphan Drug Report (2014) by Evaluate Pharma reveals that worldwide orphan drug sales will reach $178 billion by 2020. The proportion of orphan drugs in relation to the rest of the industry is also growing, with orphans set to account for just over 20% of all prescription drug sales by 2020. In 2012, orphan drugs represented 35% of all new drug output (revenue-wise), according to the 2013 Evaluate Pharma Orphan Drug Report, which also reports that, 41 of the 100 top drugs serve patient groups of 100,000 or fewer—up from just 23 in 2010. Given the small target patient population for any given orphan drug, it's not unusual for these specialized therapies to be priced between $100,000 and $400,000 per patient per year. The revenue per patient ranged between $33,000 and $220,000 for the top 20 selling Orphan drugs in 2014 by sales. Interestingly, the revenue per patient correlated (R^2=0.72) with the number of patients confirming industry perceptions that smaller patient groups allow a pricing premium to be achieved versus non-orphans.

The expected payoff after risk adjustment and accounting for time value in this example is approximately $131 million. This, however, is based on several assumptions and hence the actual revenues can significantly vary from these projections. For instance, the product's intrinsic value has been estimated while ignoring over-head costs. Historically, these costs can vary considerably between companies and market conditions. In a virtual company setup, only a small number of full-time personnel on company's payroll, lab space, equipment, and materials are required while much of the work can be outsourced to a contract research organization. In a large pharmaceutical company, the over-head costs get spread over overlapping projects. However, in a biotechnology company, these costs become part of a small number of projects.

The amount that future money loses in value each year is termed the "discount rate" or "cost of capital". Discount rate is generally the weighted average cost of capital (WACC). The WACC is calculated by taking into account the ratio of debt and equity, the rate at which capital can be borrowed, and the rate of market equity. The rate of equity in turn depends on beta (or market risk) which is determined using capital asset pricing model (CAPM) by comparing the company with similar companies that are publicly traded. For most biotech companies, debt is almost non-existent. Also, many biotechs go public while still not generating any revenue. Hence, deriving a WACC is difficult. In this example, we have used the internal rate of return (IRR) that is generally expected by the biotech investors.

The total cost of developing the product is ~$30 million. It would be grossly inappropriate simply to subtract the costs from the revenue to estimate product's intrinsic value. Such a calculation would imply that each clinical trial was a guaranteed success. However, in reality, success rates vary depending on the phase of development, therapeutic modality, and indication. Hence, accounting for this risk would better reflect upon the expected cash flows. In this model, the clinical success rates have been used to adjust the revenues. Alternatively, likelihood of clinical success can also be used (Stewart, Allison et al. 2001).

While the ultimate payoff can dramatically vary from the projections in this model, it provides a frame work to start a discussion between value generators, investors, and potential acquirers. The set of assumptions used here are subjective in nature. Also, as it is true with any financial model, the risks associated

with over-fitting the model should not be underestimated. The goal of this work is to communicate the potential market value of developing a drug to treat an orphan disease such as Dercum's disease.

REFERENCES

Devillers, A. C. and A. P. Oranje (1999). "Treatment of pain in adiposis dolorosa (Dercum's disease) with intravenous lidocaine: a case report with a 10-year follow-up." Clin Exp Dermatol **24**(3): 240-241.

DiMasi, J. A., L. Feldman, A. Seckler and A. Wilson (2010). "Trends in risks associated with new drug development: success rates for investigational drugs." Clin Pharmacol Ther **87**(3): 272-277.

Hadjivasiliou, A. (2017). Orphan Drug Report. Evaluate Pharma. L. Urquhart.

Hansson, E., H. Svensson and H. Brorson (2012). "Review of Dercum's disease and proposal of diagnostic criteria, diagnostic methods, classification and management." Orphanet J Rare Dis **7**: 23.

Herbst, K. L. (2012). "Rare adipose disorders (RADs) masquerading as obesity." Acta Pharmacol Sin **33**(2): 155-172.

Orfali, M., L. Feldman, V. Bhattacharjee, P. Harkins, S. Kadam, C. Lo, M. Ravi, D. T. Shringarpure, J. Mardekian, C. Cassino and T. Cote (2012). "Raising orphans: how clinical development programs of drugs for rare and common diseases are different." Clin Pharmacol Ther **92**(2): 262-264.

Stewart, J. J., P. N. Allison and R. S. Johnson (2001). "Putting a price on biotechnology." Nat Biotechnol **19**(9): 813-817.

Svennebring, A. M. and J. E. Wikberg (2013). "Net present value approaches for drug discovery." Springerplus **2**(1): 140.

Wortham, N. C. and I. P. Tomlinson (2005). "Dercum's disease." Skinmed **4**(3): 157-162; quiz 163-154.