

The Tale of the Golden Goose

APRIL 23, 2018

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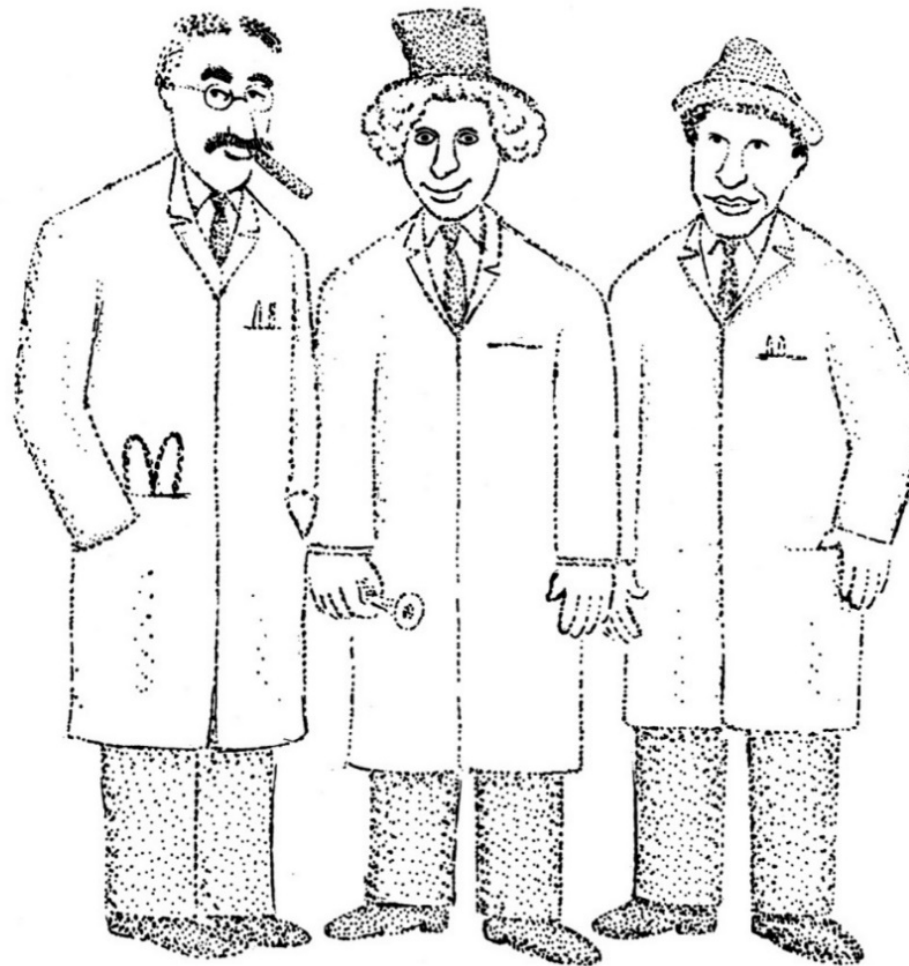
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Investing in Biotech is a Horrible Idea



- Less than 10% of companies are profitable
- 'Hopes and dreams' multiples
- Poor reimbursement potential
- 90% clinical failure rate
- Twitter leads to more volatility than clinical trials

The Experts

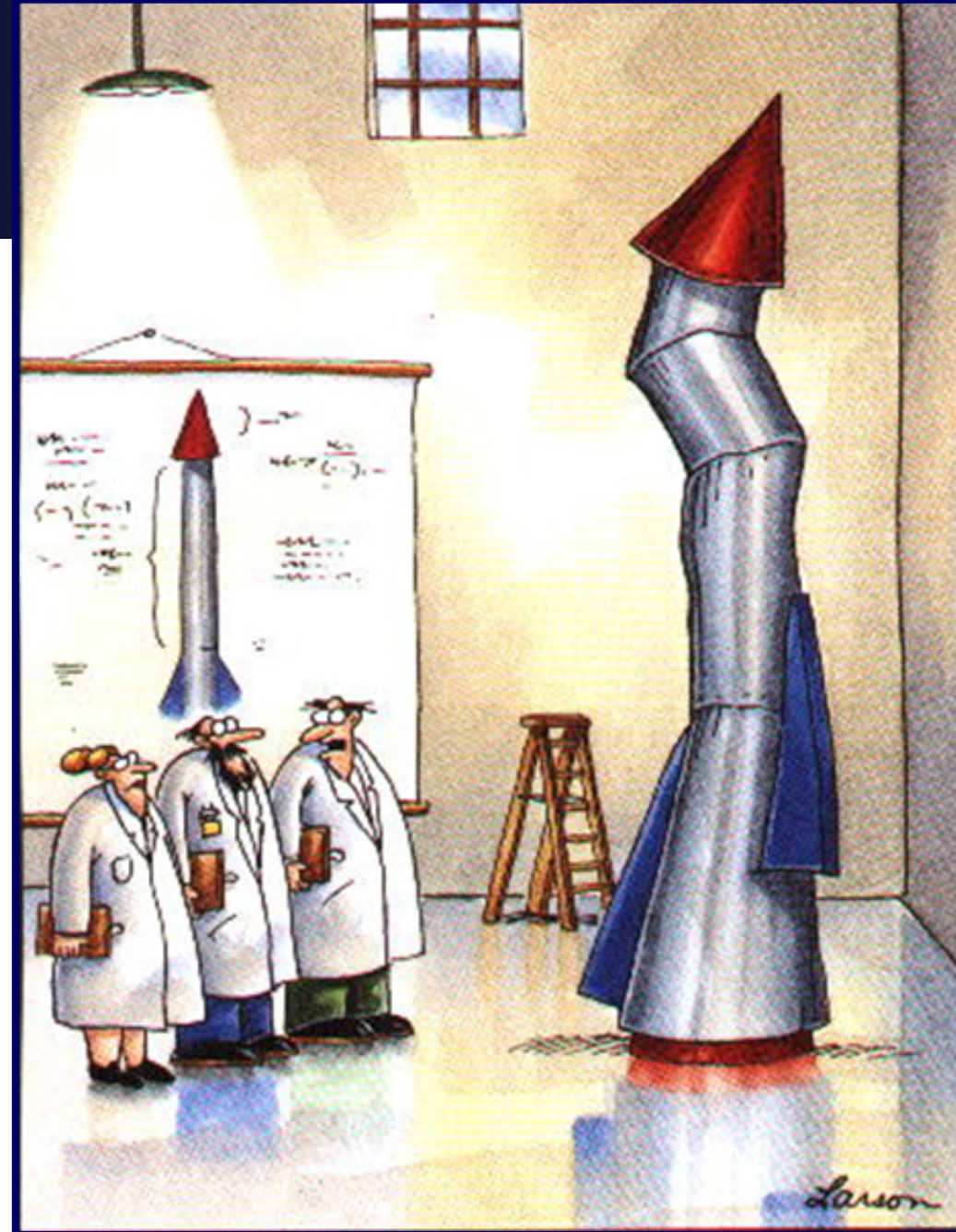


MANKOFF

Three Out of Four Doctors

Circle of Competence

*“It’s time we face reality, my friends...
We’re not exactly rocket scientists.”*



Size Matters



Ascendis Pharma (Nasdaq: ASND)

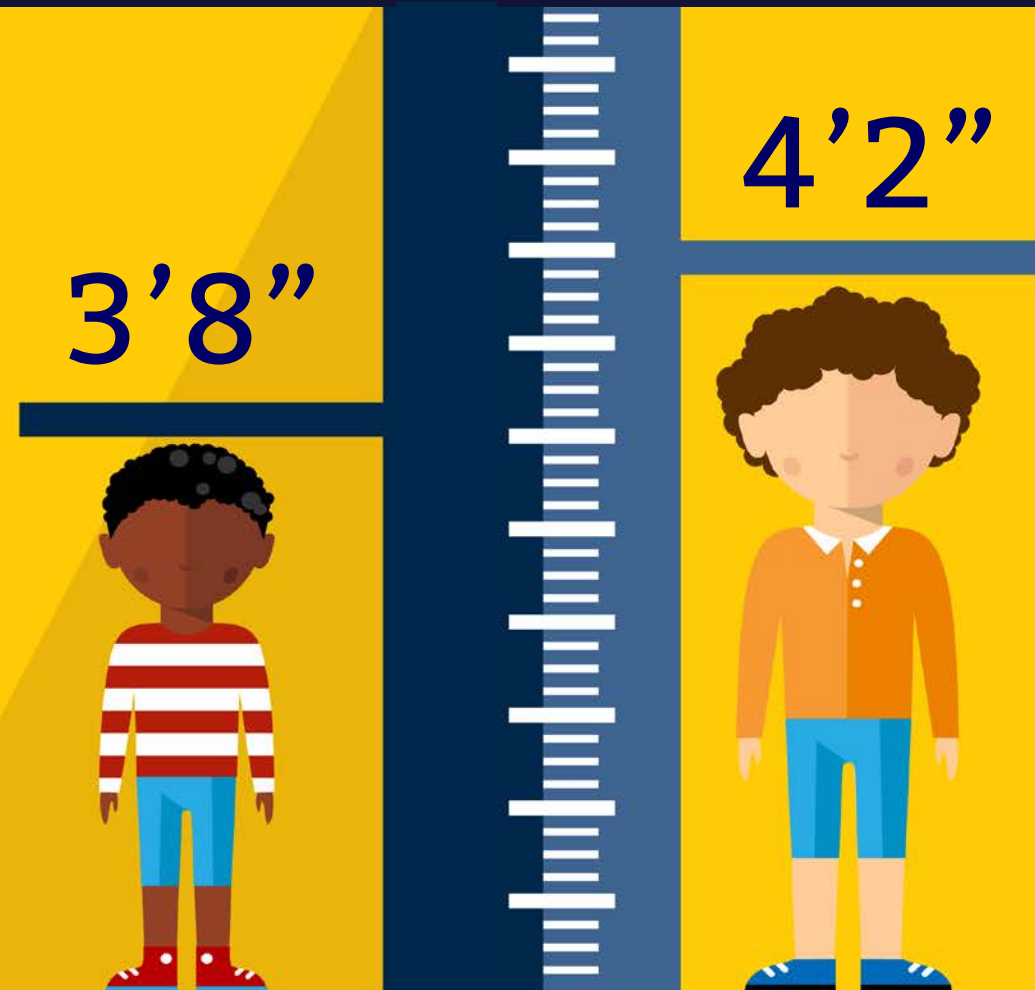


¹ As of Market Close, April 17, 2018

Ascendis the Golden Goose



Growth Hormone Deficiency



Growth Hormone Approved in 1985

Media / Press Releases



Friday, Oct 18, 1985

FDA Approves Genentech's Drug to Treat Children's Growth Disorder

South San Francisco, Calif. -- October 18, 1985 --

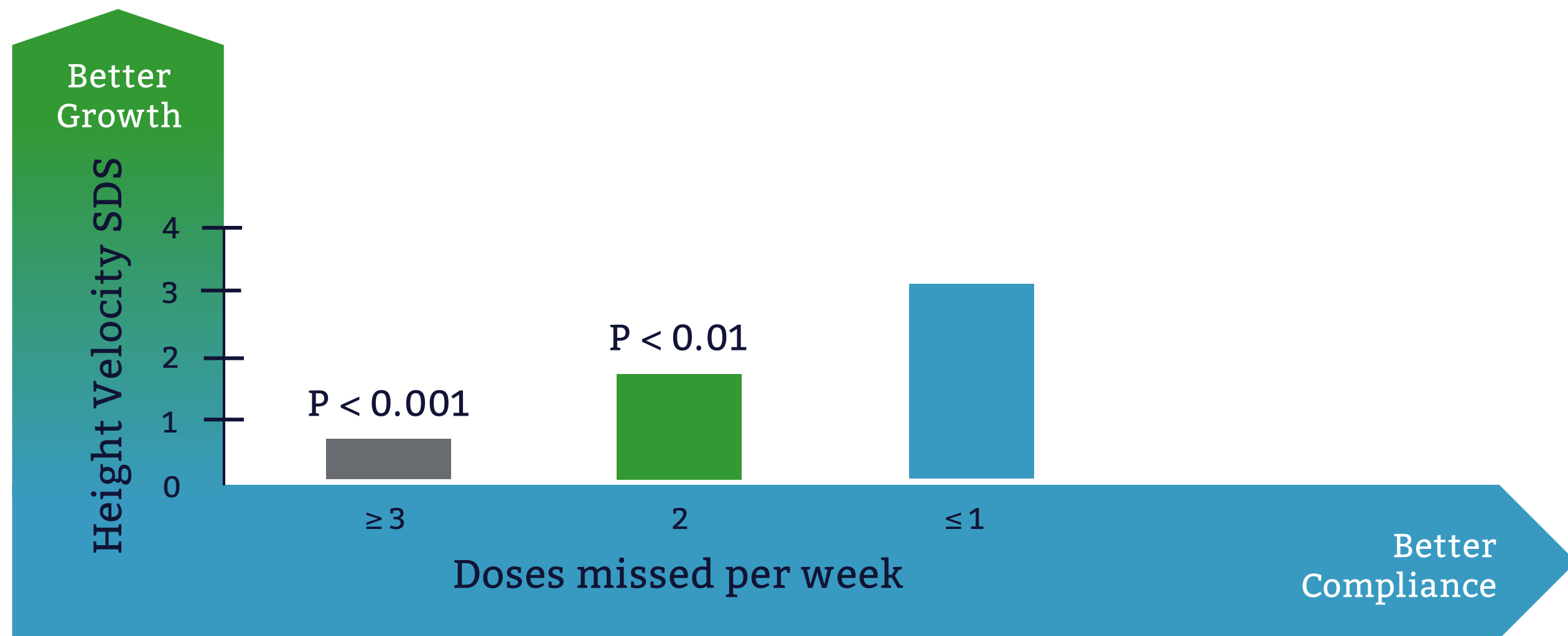
The Food and Drug Administration today approved Genentech's first human pharmaceutical, a biosynthetic growth hormone for treating severely growth retarded children.



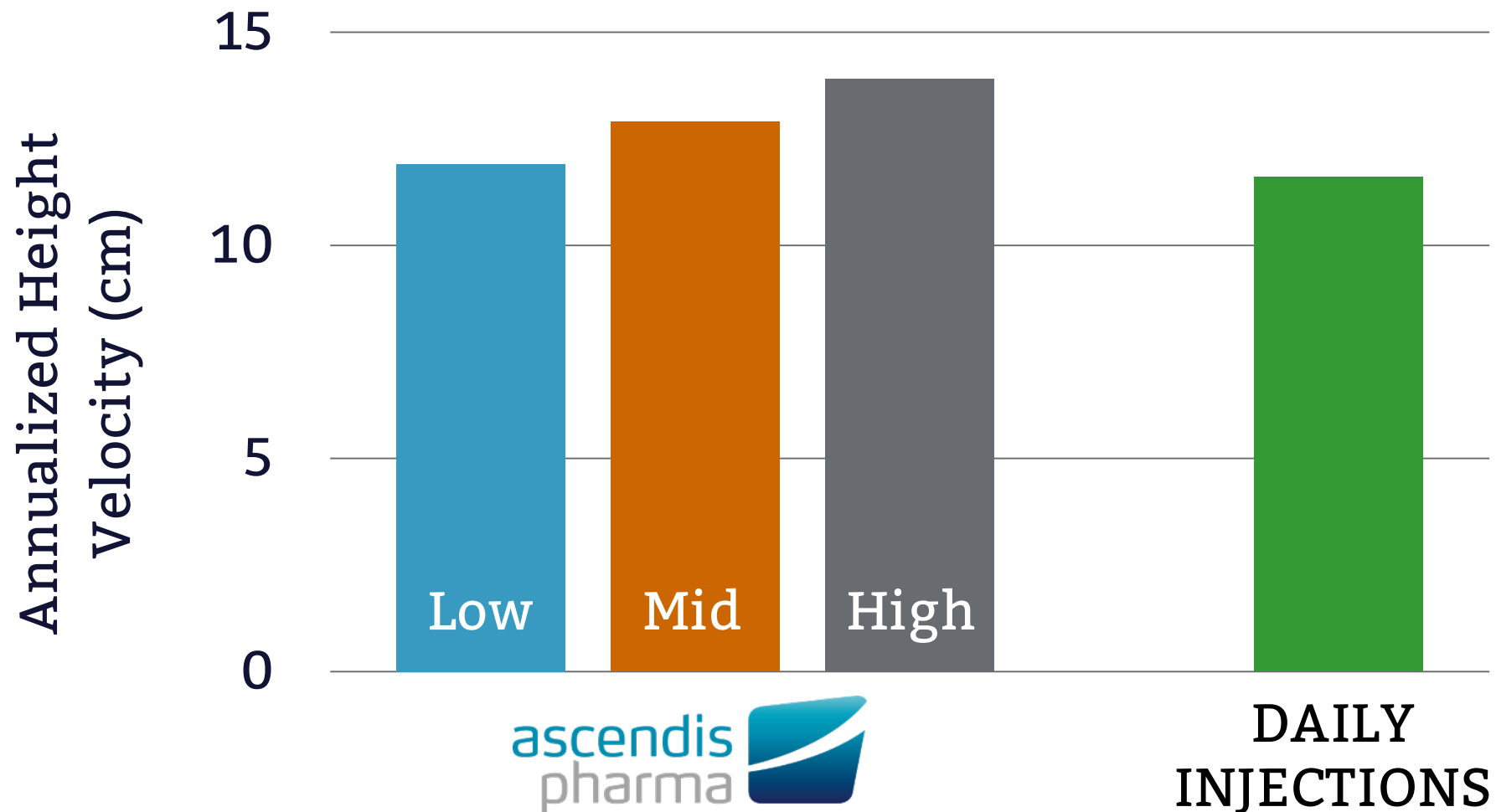
You think making your kid eat broccoli is hard?



Drugs Only Work If You Use Them! (duh)...



Growth Hormone Makes Kids Taller

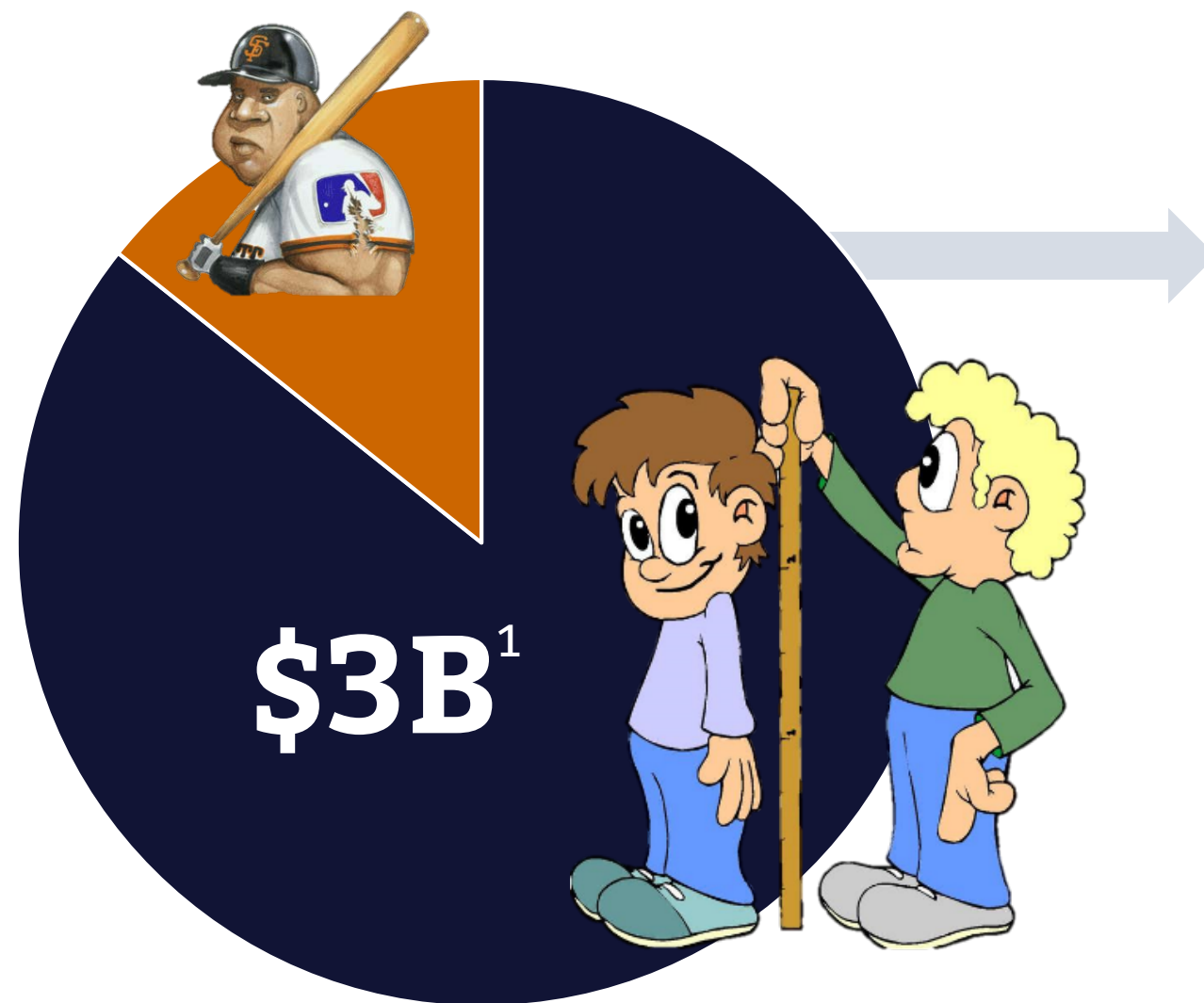


Dosed Only
1X
PER WEEK!

Outgrowing the Competition

	Efficacy : <i>Growth Rate Comparable to Daily Injections</i>	Safety : <i>Safety Profile Comparable to Daily Injections</i>
	✓	✓
	✗	✗
	✗	✗
	✗	✓
	✗	✓
	✓	✗

\$3+ billion market



**NET PRICE: \$35K/yr (US & Japan),
\$20K/yr (EU)**

PEAK PENETRATION: 50%

AVG DURATION OF THERAPY: 8 YRS

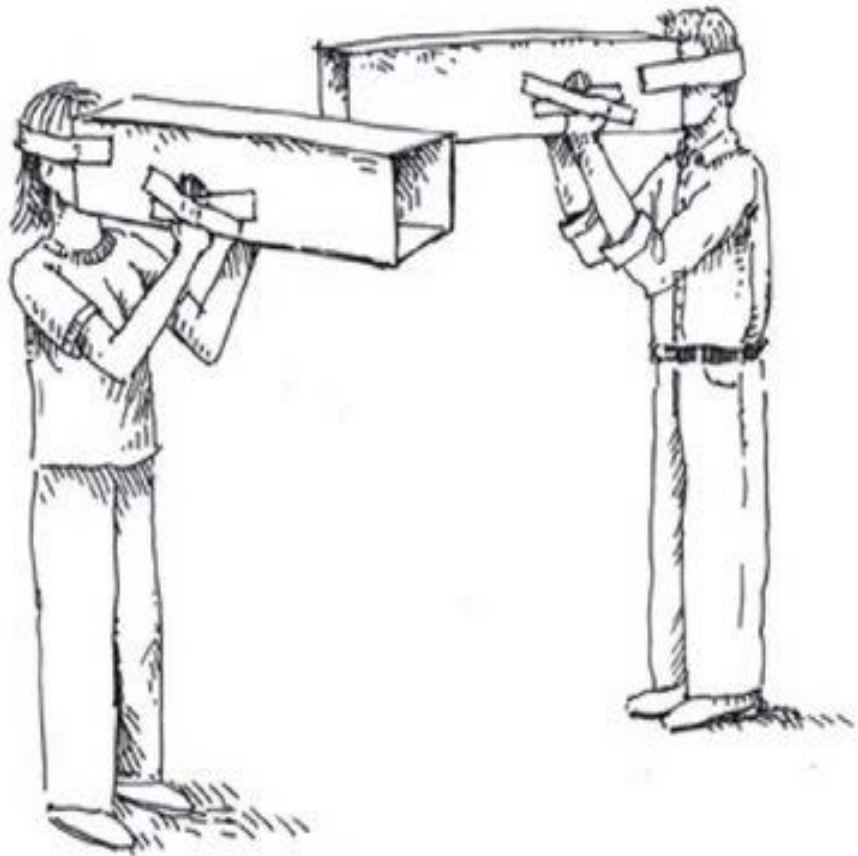
PEAK REVENUE: \$1.5B

Ascendis Will Eat Big Pharma's Lunch



\$129¹ /share
(4x peak revenue)

Biotech Investors = Myopic Focus



“We’re buying the company, the brand, the building ...
but mostly we’re buying the golden eggs.”

Proven Target = Higher Probability

Preclinical

Phase 1

Phase 2

Phase 3

Pediatric Growth Hormone Deficiency (GHD)

Adult GHD

Hypoparathyroidism (PTH)

Achondroplasia

Genentech

*Ophthalmology*¹

SANOFI

*Diabetes*¹



Growth Hormone's Side Kick - Achondroplasia



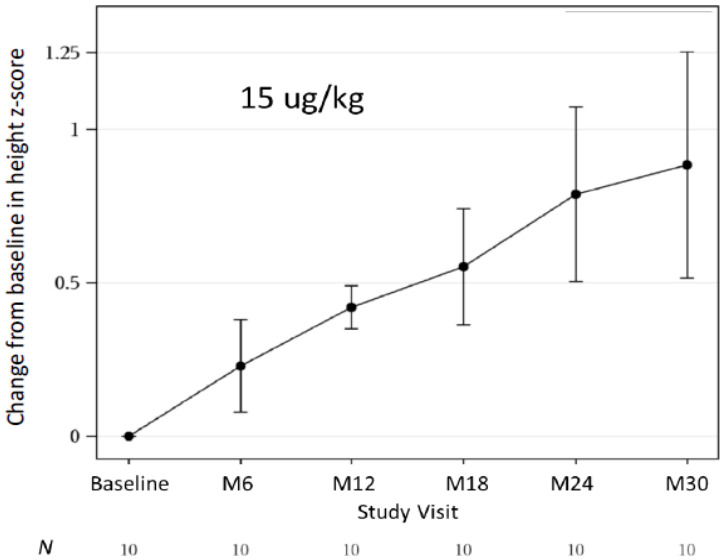
BioMARIN

R&D Day 2017

Durable Growth Effects in Children with Achondroplasia Treated with 15 ug/kg Vosoritide for 30 Months

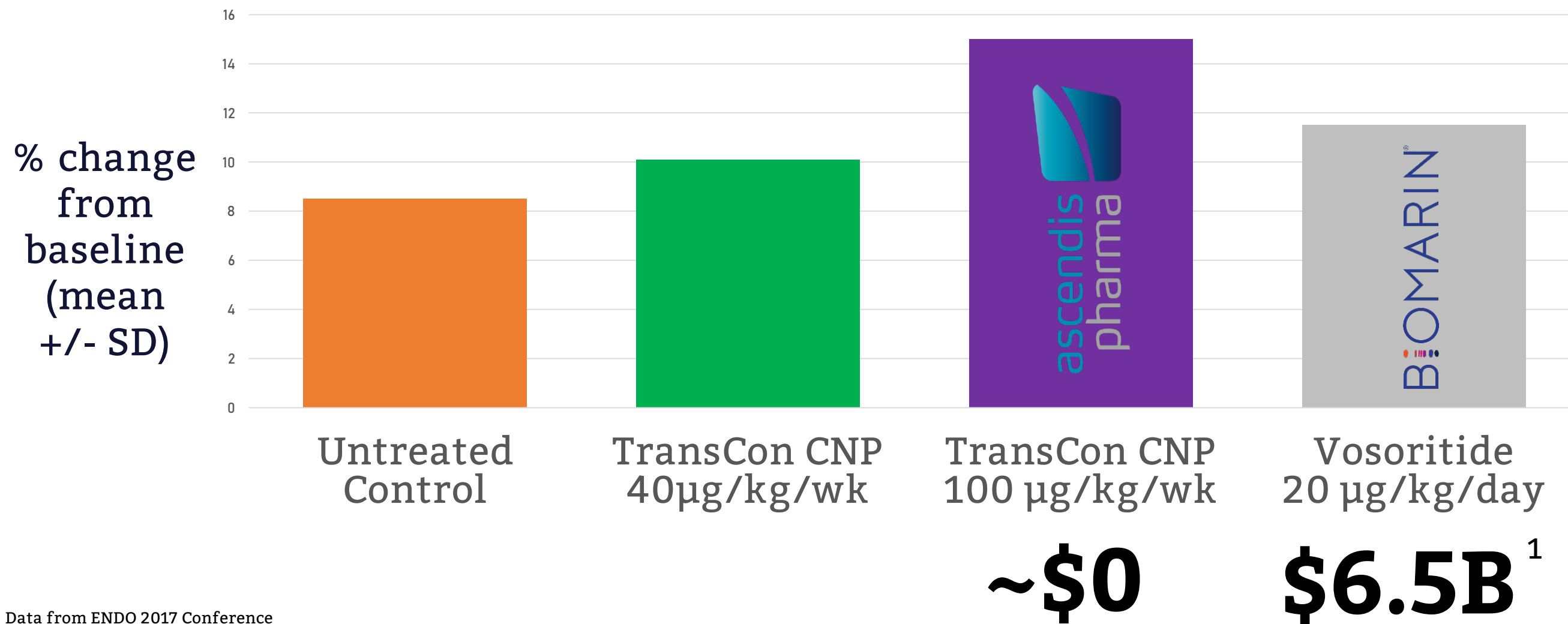
N=10	Baseline	6 mos Δ	12 mos Δ	18 mos Δ	24 mos Δ	30 mos Δ
Z-score (SDS)	-4.6 (1.14)	0.2 (0.15)	0.4 (0.07)	0.6 (0.19)	0.8 (0.28)	0.9 (0.37)

Table date = mean (SD)



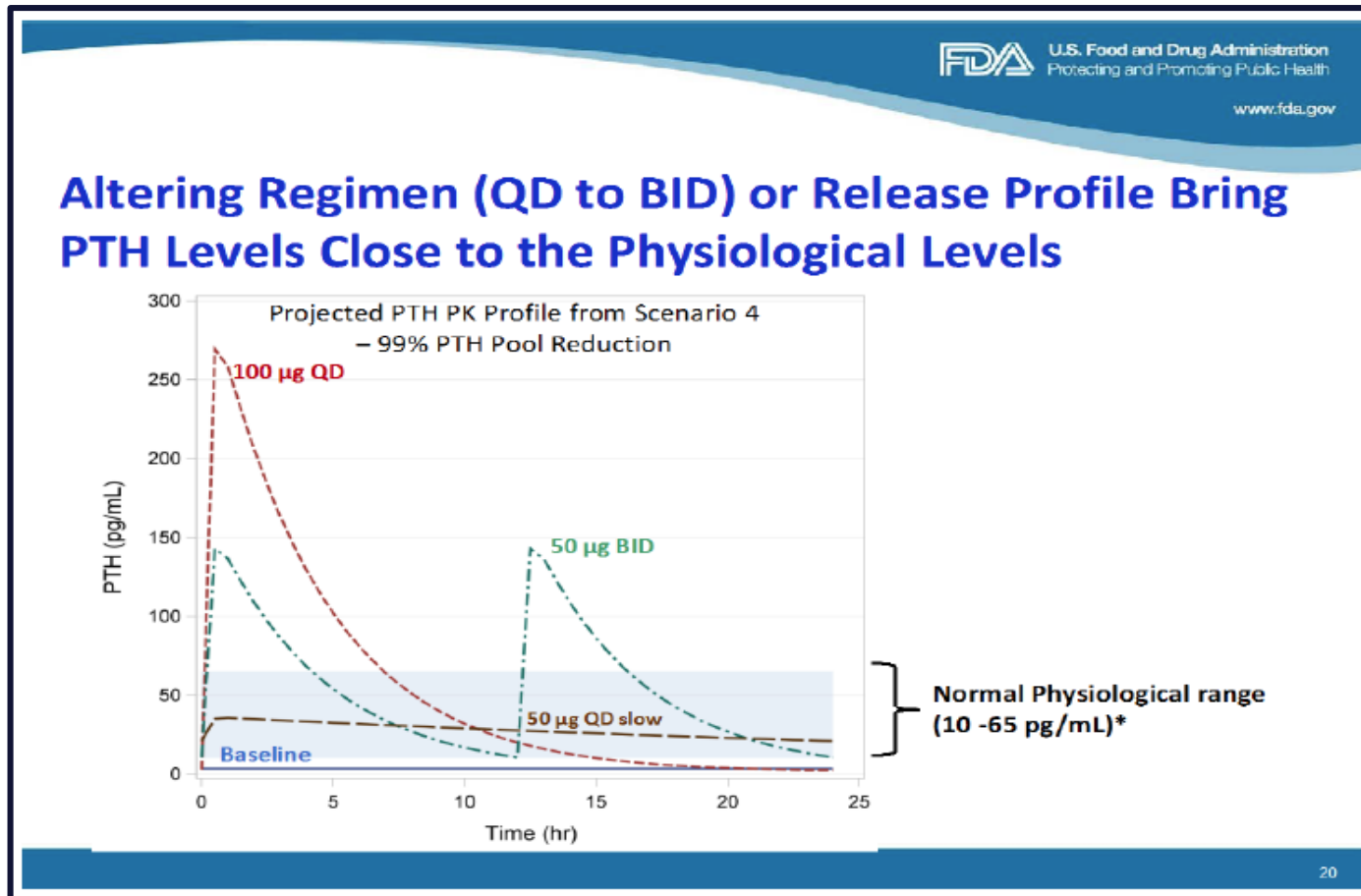
*Whisker bars represent one standard deviation above and below mean

Winning Head-to-Head



Data from ENDO 2017 Conference
1 Cowen and Company Equity Research, as of April 17, 2018

Hypoparathyroidism (PTH)



1

Shire **Natpara[®]**
(parathyroid hormone)
for Injection
25 • 50 • 75 • 100 mcg per dose strength

\$2.6B²

¹ FDA Briefing Document, Endocrinology and Metabolic Drugs Advisory Committee Meeting, September 2014

² NPS Pharmaceuticals Inc. (NASDAQ: NPSP) 14D-9. Filed with SEC, 1/23/2015.

Risks of Biotech Investing

Warnings

Company

Ascendis

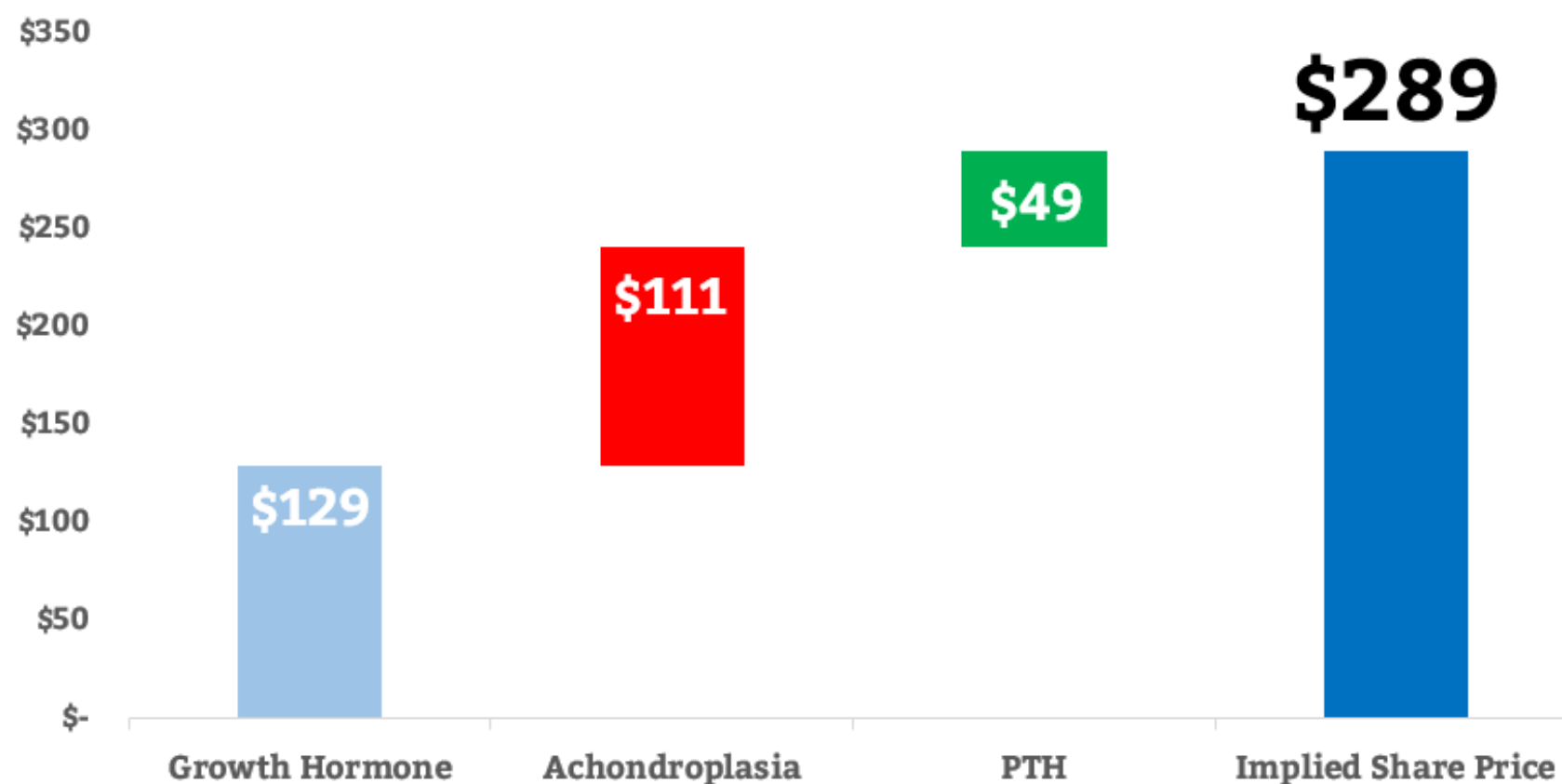
TransCon Growth Hormone.....0.24mg/kg/wk

- Biotech investing may cause anxiety and reduced ability to sleep through the night.
- Immediately after investing, you may experience sudden volatility in the stock due to headline risk from competitors.

CONSULT WITH YOUR INVESTMENT TEAM BEFORE INITIATING A POSITION IN ASCENDIS

- Utilization of PEG with growth hormone has been associated with toxicity for other companies. Ascendis' PEGylation strategy is fundamentally different from all prior programs, but a theoretical risk remains.
- Ascendis has no recurring revenue. Dilution from future equity offerings may occur. If a secondary offering occurs, please contact the Ascendis management team immediately to discuss placing an order.
- There is no guarantee that past clinical studies will result in successful future studies. The data for Ascendis' long-acting growth hormone approval study is expected in early 2019 and may cause a dramatic change in stock price.
- Ascendis has never submitted an NDA (new drug application) before. While the management team has successfully developed drugs before at other companies, this does not ensure future success.
- Possible difficulties or delays may arise from manufacturing.

Implied Fair Value Of \$289



- Trading below margin of safety based on one asset
- Long-acting growth hormone threatens \$3B in pharma revenue making Ascendis an obvious acquisition target
- Early pipeline is a Golden Goose - not valued by Wall St, but worth >\$7B in upside (+\$160/share)

1. EcoR1 Capital Logo

My name is Oleg Nodelman and I am the Founder and Managing Director of EcoR1 Capital, a San Francisco-based, value-oriented biotech focused investment fund. Thank you to the folks at IRA SOHN for having me here, and for your efforts with such an important cause. ///

2. Disclaimer ///

3. Investing in Biotech is a Horrible Idea

Investing in biotech companies is easily in the top 5 of worst ideas, sandwiched somewhere between eating tide pods on one end, and investing in tulips and cryptocurrency on the other.

In biotech:

- Valuations are based on hopes and dreams vs. fundamental value, and less than 10% of the sector is profitable
- The underlying science is often complicated and unpredictable

- When a company is lucky enough to get a drug approved, it has an average of 9 years of exclusivity, so rather than a castle with a moat, they have a melting ice cube
- Success is often idiosyncratic and not repeatable, so these are not companies that you can buy and hold forever ///

4. Doctors

Many folks who we see investing in biotech are PhDs and MDs who are betting on biology. There are certainly some who can make money that way, but

overall I think it can be a dangerous way to invest because the science isn't nearly as predictable as folks think. I know that because of the volatility that we see in the sector. If the science was predictable these stocks should trade more like utilities. ///

5. Rocket Scientists

At EcoR1 we start our analysis by focusing on opportunities with a discernable margin of safety based on patterns that we have identified over years of biotech investing experience. In terms of understanding the assets, we are one of the few

biotech focused funds not managed by PhDs or MDs, which for us means that we don't fall in love with the science. Instead we have fluency for the **language** of biotechnology that serves as a filter. We often invest in companies that are unfollowed, unloved, misunderstood or left for dead and that have great downside protection. These are extraordinary companies that have found themselves in an extraordinary time. ///

6. Size Matters

Today, I am here to tell you about something that George Costanza knows. That Donald Trump knows. And that Napoleon knew. And despite what your mother told you, most of you know. Size matters. We are going to talk about height... I am going to tell you about a company working in the endocrinology space, with a lead drug candidate to help patients lacking enough hormone to grow. ///

7. Introduce Ascendis

Ascendis Pharmaceuticals is a **\$2.7B** market cap Copenhagen-based biotech. Ascendis has a platform technology that enables them to modify proven drugs to enable less frequent dosing or improved efficacy. Pharma giants Genentech and Sanofi validated this delivery technology – called TRANSCON - by shelling out nearly \$100M for access to the technology. The company has \$485M in cash, which should last them for **3** or more years, although they may never need to raise money again. Ascendis'

lead asset will be on the market in 2 years and alone is worth twice the company's current market cap. ///

8. Golden Goose

Even better, Ascendis is a golden goose... a true platform company which means their delivery technology can be used again and again on dozens if not hundreds of drugs. Ascendis is a company that could keep laying golden eggs – and at this valuation we get the pipeline – which based only on the disclosed programs could be worth another 5X from here - for free. ///

9. Introduce Growth Hormone Deficiency

The company's lead drug is in late stage clinical development for the treatment of growth hormone deficiency. This is a condition where children do not produce adequate levels of hormone to grow. Specifically, diagnosed kids fall 2 standard deviations below the mean height expected for age and gender, and are confirmed to have deficient levels of growth hormone with a lab test. Left untreated, these children never experience normal growth, and will not reach typical height. There is one important term

to understand before we discuss growth hormone drug development. Annualized height velocity refers to how much a child grows in one year. In order to get approval for the treatment of growth hormone deficiency, a company needs to prove their drug causes an improvement in annualized height velocity. ///

10. Genentech History

Let's start with our margin of safety at Ascendis. To understand that, we actually need to take a quick detour back into the early history of the biotech

industry. Genentech's first-**ever** approved drug was for the treatment of growth hormone deficiency and was approved in 1985. Since then, tens of thousands of children with growth hormone deficiency have been successfully treated. Thanks to this extensive data set, we know replacing growth hormone in children who do not have adequate levels is a safe and effective therapy. Ascendis is employing *exactly* the same strategy as that FDA-approved Genentech drug, and again, we've known this strategy works for the past 33 years! ///

11. Russian Women's Track and Field

If you're still not convinced, one quick look at the Russian Olympic Contingent should once-and-for-all prove to you growth hormone works pretty darn well... ///

12. Vegetables

But what I've told you so far begs an obvious question. Why in the world do we need this drug if we've already got one from the mid 1980's that works so well?? The major issue with currently

available drugs is that they require an injection every single day. The parents in the audience will appreciate, and I know this well as the proud father of twin girls, it's nearly impossible to get your kids to eat their vegetables or take a bath. Now imagine adding a nightly injection into that routine for a decade or more... ///

13. Compliance Data

Large real-world data sets have shown that two-thirds of parents admit to skipping one or more doses per week in the first year, and compliance only

gets worse with longer-term dosing. You can see here that missing just 2 or more doses per week causes statistically significant inferior growth. And you really don't need much data or an MD or PHD to be convinced that if you don't take your drugs, they won't work! ///

14. Efficacy Slide

Ascendis has generated robust clinical data comparing their weekly drug head-to-head versus the daily injection standard of care. In their clinical study, three different doses of the Ascendis drug

were tested, and all three showed better growth than daily injections. Importantly, the Ascendis drug was safe and well tolerated. To get the drug approved, all Ascendis has to do is replicate this data in their current phase 3 trial and show that their drug is *not inferior* to the daily option. The technical statistics plan calls for the lower bound of the two-sided 95% confidence interval of the difference between Ascendis' drug and the daily injection be less than 2cm. All that statistical jargon basically means the Ascendis drug can actually show slightly

numerically *worse* growth than the daily arm and still get FDA approval. And remember, Ascendis has already shown 3 different doses and all were *better* than the daily option. ///

15. Competition Slide

Now, it's not a novel insight parents and patients prefer once-weekly dosing to a daily injection. This was so obvious to drug developers they set out on the quest for a less frequent dosing option immediately after the first approval back in 1985. But every competitor has failed. All of those

programs made a common mistake. Growth hormone is an endogenous hormone, meaning it's natural – our bodies produce it. The competing programs pursuing a less frequent dosing option made permanent modifications to the hormone. Ascendis TRANSCON, however, enables them to deliver unmodified, natural growth hormone. That way, the receptors in our body that bind growth hormone see the exact same unmodified hormone that our bodies produce naturally. Ascendis is the

first and only less frequent dosing program with the technology to enable this. ///

16. Big Market

Barry Bonds, frat guys, and other doping athletes account for some growth hormone use, but the current total branded market for growth hormone is \$3B in annual revenue, and growing. We don't think abusers will care much about less frequent dosing, nor will they have access to the new product. But according to our primary research and interviews with pediatric endocrinologists, we anticipate nearly

all physicians treating growth hormone deficient children to switch to the Ascendis drug when available. But to calculate our conservative scenario, we assume it captures only 1/2 of that \$3B market, implying peak annual sales of about \$1.5B. And despite the superior product Ascendis is developing, we assume they price their drug at parity with daily hormone. ///

17. Eating Big Pharma's Lunch

Remember that big pharma has been selling daily growth hormone for decades. And big pharma does

not like having their lunch eaten out from under them. There is a precedent in other therapeutic areas for the introduction of a great long-acting alternative cannibalizing the standard of care. We think once Ascendis launches their long-acting product, pharma companies with billions of cash flow at stake will not sit idly by. There are almost 10 relatively obvious buyers for a long-acting program. M&A buyers often think in terms of multiples of peak sales. For example, earlier this month Novartis purchased AveXis, a one-asset rare disease company

with no pipeline for 4x peak projected sales. Using that same 4x peak projected sales, we find an M&A clearing price of \$129/share for JUST THE Ascendis growth hormone program. ///

18. Myopic Focus

So, we have a biotech company that trades below its margin-of-safety case on one asset alone. Sounds great, but it gets better when you realize we haven't even talked about the pipeline yet. A common bias among investors looking at biotech stocks is to myopically focus on the lead asset, and pay no

attention to the remainder of the pipeline. This often creates opportunities for free call options, which present pure upside for our investment. With Ascendis, you buy the lead asset for half off, and get the Golden Goose for free. ///

19. Improved Probability of Success

Now, investors often place no value on early stage assets, like the ones called out on this slide, for good reason. Success in biotech is often idiosyncratic and drug development is hard and risky, so it's usually a safe assumption that few if any early stage assets

will work. Success with Ascendis' drug development strategy may change that narrative. Remember, Ascendis is applying their platform technology to drugs *already proven to work*. So their candidates have a much higher probability of success than industry averages. ///

20. Growth Hormone's Side Kick - Achondroplasia

The first free call option or golden egg at Ascendis is for the treatment of achondroplasia, which is the most common form of dwarfism, and perfectly situated within the company's expertise on growth

related disorders. Achondroplasia patients are born with hypotonia, often referred to as floppy-baby syndrome. Around 8 years of age, bowing and instability of the knees is common. As they enter teenage years, achondroplasia patients can suffer from spinal stenosis, or narrowing of the spinal canal. This can result in serious morbidity, including shooting pains, difficulty walking, numbness in limbs, loss of bladder control and sexual dysfunction. Perhaps the most famous example is Verne Troyer, the actor who played Mini-Me in Austin Powers.

BioMarin Pharmaceuticals is also developing a drug for these patients, and has already demonstrated proof of concept. However, their drug causes hypotension when dosed, and only lasts in the body for a few minutes, muting its efficacy. Ascendis has modified this drug to avoid the hypotension safety issues, and extend the time the drug persists in the body to enable better growth. ///

21. Winning Head-to-Head

Ascendis is so confident in their platform, they tested their drug head-to-head against BioMarin's in

primates. You can see the purple bar is the Ascendis candidate, the grey bar is the BioMarin drug, and along the y-axis is a measure of growth. The Ascendis candidate demonstrated a robust improvement in efficacy vs BioMarin. Importantly, the BioMarin drug is injected daily, while Ascendis is only **once per week, just like Growth Hormone**.

It can be challenging to value an early stage drug like this one. We typically use a bottoms up approach and assume a modest penetration rate. Another method that we seldom employ is relative valuation

analysis. In this case, since their competitor is so well followed – one exercise is to look at how much value analysts attribute to the BioMarin program Vosoritide. Sell-side analysts attribute \$6.5B in value to Vosoritide, and nothing to TRANSCON CNP. And remember, you are looking at the head-to-head data suggesting Ascendis has the best-in-class drug. ///

22. PTH

The second call option or golden egg is for the treatment of hypoparathyroidism, or PTH. Roughly 80k patients per year in the US are diagnosed with

PTH, most commonly resulting from thyroid or head and neck surgery. Patients who do not have adequate levels of parathyroid hormone experience chronic fatigue, cramping, chest pain, inability to concentrate or focus, and often progress to kidney disease. In 2015, the FDA approved the first drug for the treatment of PTH, called NATPARA. However, the regulators went out of their way to caveat their approval with concerns that the drug was suboptimal. They noted the drug was only present in the body for 12 hours after each injection, leaving

patients covered for only half the day. Ascendis has improved this drug to enable a full 24 hours of coverage for patients.

Again, to value this drug, we are able to use comparables, although the DCF analysis isn't much different. Shire acquired NPS Pharmaceuticals, the company developing NATPARA in 2015, and attributed \$2.6B in value to this asset. We believe the Ascendis product may be a vast-improvement over NATPARA, and still, analysts ascribe little value to the program. ///

23. Risks of biotech investing

And now, the obligatory safety warning: Ascendis is not for everyone. You should consult your biotech analyst before purchasing Ascendis. Initiating a position may cause increased anxiety and reduced ability to sleep through the night. Serious, sometimes precipitous, drops in stock prices occur in biotech. Immediately after investing, you may experience sudden volatility due to headline risk from competitors. If stock declines are experienced

for no fundamental reason, call your broker immediately to increase your position.

Rare, but serious safety concerns have arisen in other companies' late stage clinical development programs. While no safety concerns have occurred with any Ascendis clinical programs to date, they may in the future. The use of PEG to extend the half-life of drugs has been historically associated with toxicity. While the Ascendis PEGylation technique is fundamentally different from all prior attempts and the company has thoroughly investigated this, a theoretical risk with the use of PEG remains.

Ascendis has no marketed products, and thus no recurring revenue. Dilution from equity offerings may occur. In the event of a secondary offering, immediately schedule a call with Ascendis management team to discuss placing an order. There is no guarantee past successful clinical studies will be replicated. The data from the approval study of Ascendis' long-acting growth hormone is expected in early 2019 and may cause a dramatic change in stock price.

Ascendis has never submitted a new drug application to the FDA, and thus may have difficulties with the filing. While the management team has successfully brought drugs to market in prior roles, this does not ensure success in the future. They may experience difficulties or delays with manufacturing. ///

24. Price Target of \$289/Share

So in summary, we have a lead drug nearing approval worth 100% more than the value of the

company. This asset happens to threaten \$3B of big pharma revenue which makes Ascendis an obvious acquisition target. Close behind that, we have two assets completely ignored by analysts, both using mechanisms already proven to be effective in humans. Using a sum of the parts valuation methodology, we believe Ascendis could be worth \$289/share, or nearly 5x from where the stock is trading. And this isn't just another fairy tale! ///