Wall Street On Defining Clinically Meaningful Effect (CME)

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Table of Contents

Pragmatic players

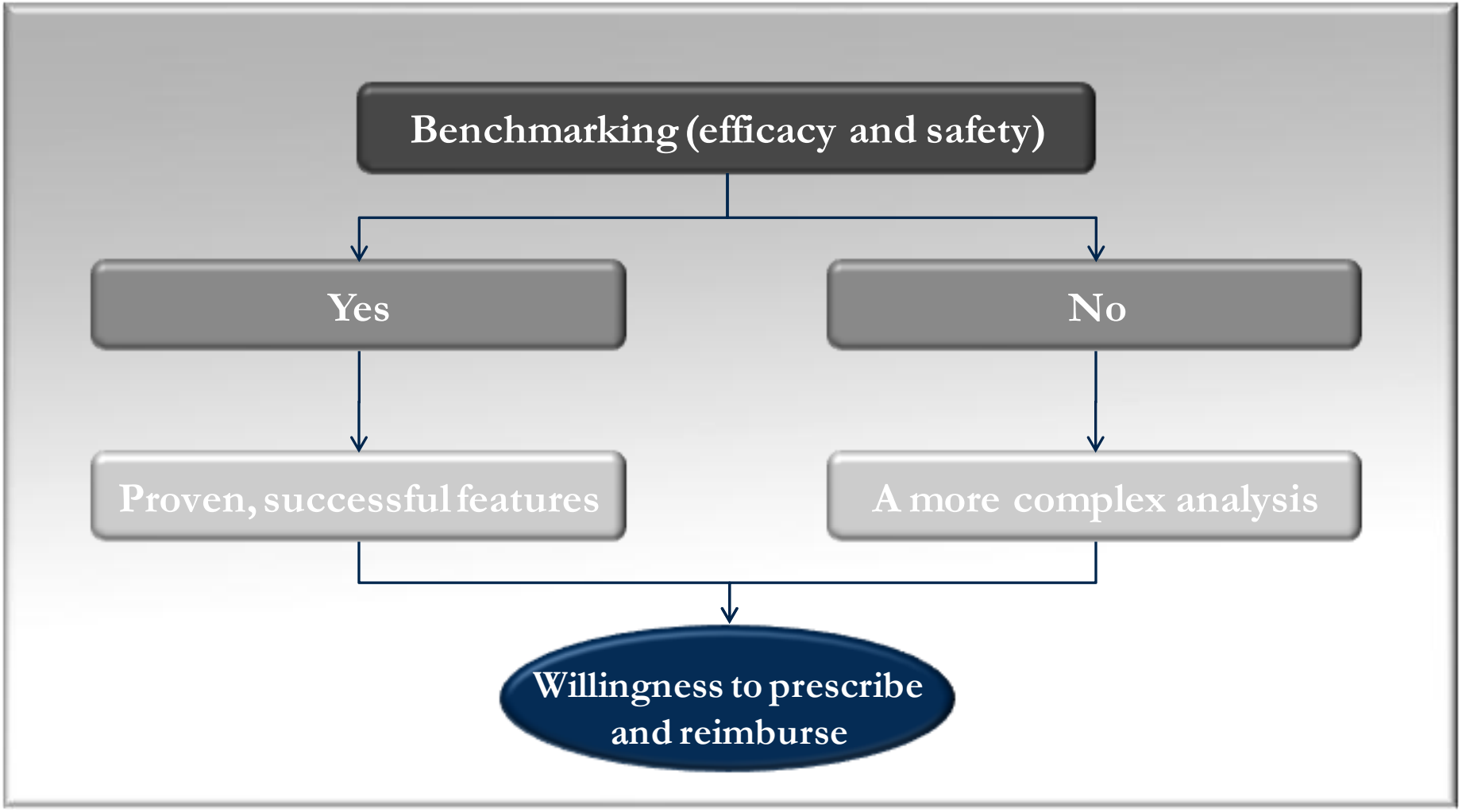
Most imperfect knowledge

Most macro perspective

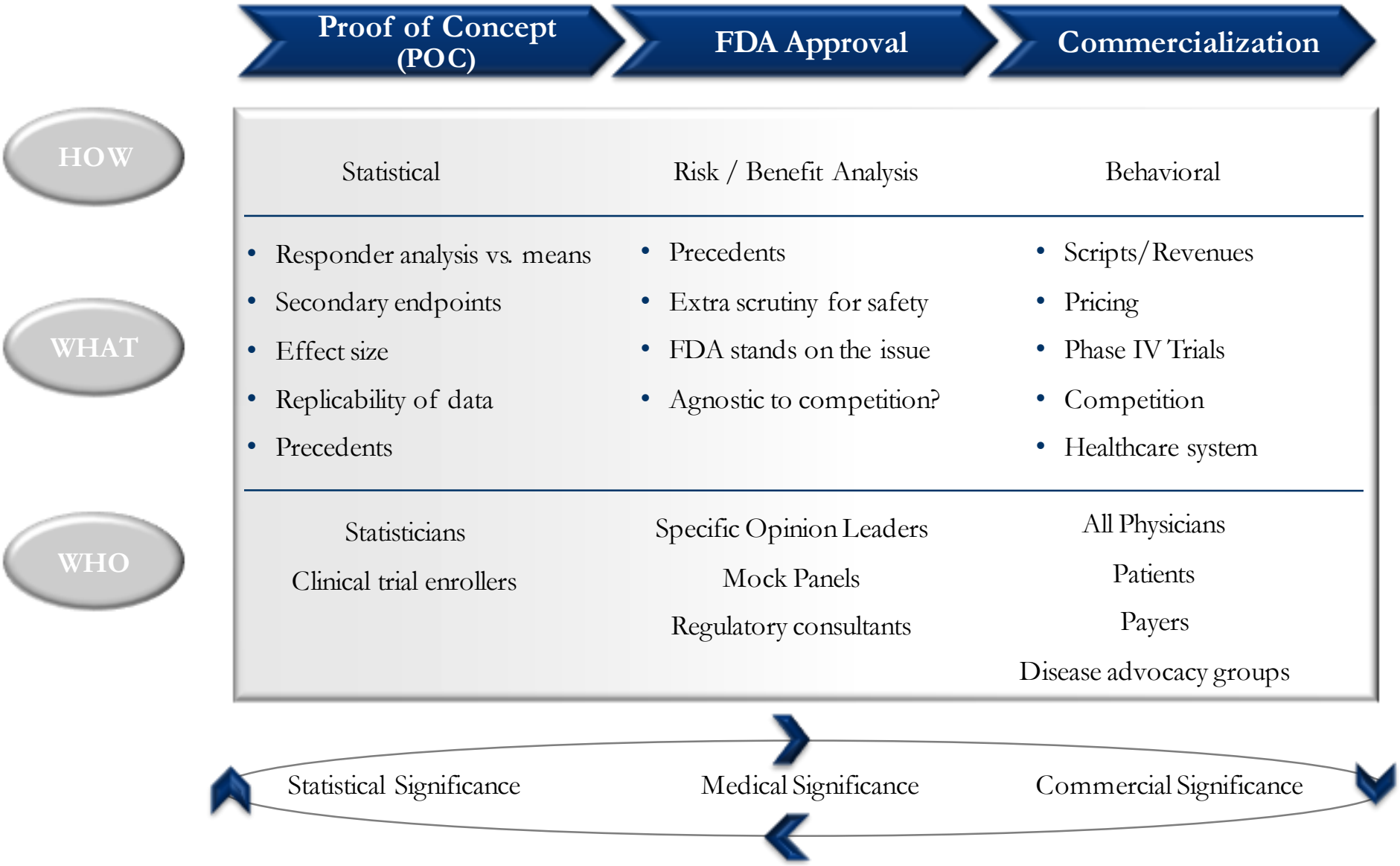
- Motivation: Positive Returns
- Manage risk and allocate capital … in real time
- Event driven mentality

= The Most Pragmatic Approach

It all starts with benchmarking



The How, What and Who of Wall Street's thinking in the CNS space



Wall Street's general points of agreement

1. Mean difference analyses are fine in well understood models (MADRS, UPDRS)
2. Responder analyses tell you more (for indications with fewer precedents)
   Caveat: Definition of responder needs to be good
3. Functional endpoints / daily activity / and quality of life endpoints give validity to "confusing" endpoints
4. Use of Co-primary endpoints may strengthen perception of CME
5. Validation by KOL is key in any step of the process

Wall Street's general preferences of a CME (observations)

Scales used or definition of "responder" are often designed for regulatory reasons (to reduce variability)	Regulatory constrictions often preclude the demonstration of CME
In heterogeneous diseases (any) there is always a group that benefits greatly (how to define it?)	Trials against placebo good for approval (not for CME)
A positive results driven my few items within a scale is a red flag	PRO guidance has been helpful but physicians based instruments prevail
New mechanisms of action get special bonus (open new treatment modalities)- (TC-5214)	A safety advantage has to be strong and relevant (and measurable?)

Case Study #1: Ampyra

Walking ability in people with multiple sclerosis (MS)

ENDPOINT

Timed 25-Foot Walk: A responder was defined as a patient who showed faster walking speed for a least three visits out of a possible four during the double-blind period than the maximum value achieved in the five non-double-blind no treatment visits (four before the double-blind period and one after).

RESULTS

Responder Analysis:

- 34.8%vs. 8.3% $p < 0.001$ (666% stock appreciation) ($300 million MCAP)
- 42.9% vs. 9.3% $p < 0.001$ (44% stock appreciation) ($930 million MCAP)

Commercialization

- Approved in early January 2010 (60% stock appreciation) ($1.1 billion MCAP)
- 2011 Revenues: $210 Million
- 2012 Revenue Guidance: $255-$275 Million
- MCAP $1.05 Billion

Perception of its Medical Utility Has Evolved Overtime

Case Study #2: Viladozone

Major Depressive Disorder (MDD)

ENDPOINT

- Montgomery-Åsberg Depression Rating Scale (MADRS) :

RESULTS

- LS Mean (95% CI) difference from **placebo** in change from baseline
- -3.2 (-5.2, -1.3)
- -2.5 (-4.4, -10.6)

Commercialization

- Approved in January 2011 (72% appreciation; MCAP $1.1 Billion)
- Sold to FRX for $1.2 Billion
- Launched in August 2011
- 2011 Revenues: $20.1 Million
- 2012 Revenue Guidance: NA

Average Efficacy/Safety advantage?

Case Study #3: Droxidopa

Neurogenic Othostatic Hypotension (NOH)

ENDPOINT

- Orthostatic Hypotension Scale (OHQ)-6 symptomatic domains 4 functional domains
- Dizziness was the original endpoint

RESULTS

- Mean reduction in OHQ scores vs. placebo/ not a responder analysis
- 0.9 points delta vs. placebo ($p<0.01$): FDA asking about the clinical significance of this
- 39% ($70 million) appreciation (MCAP $240 million)

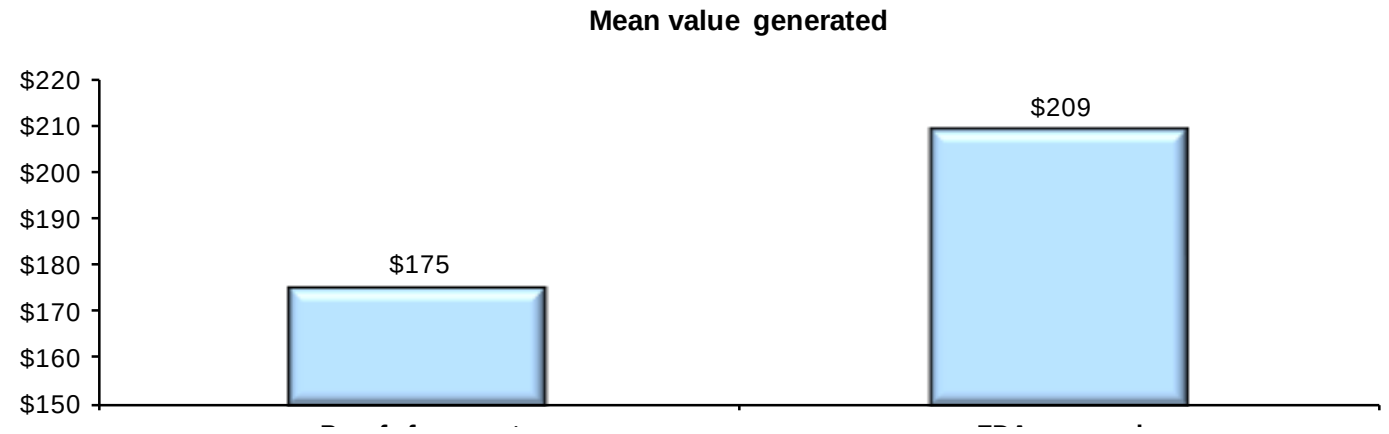
FDA

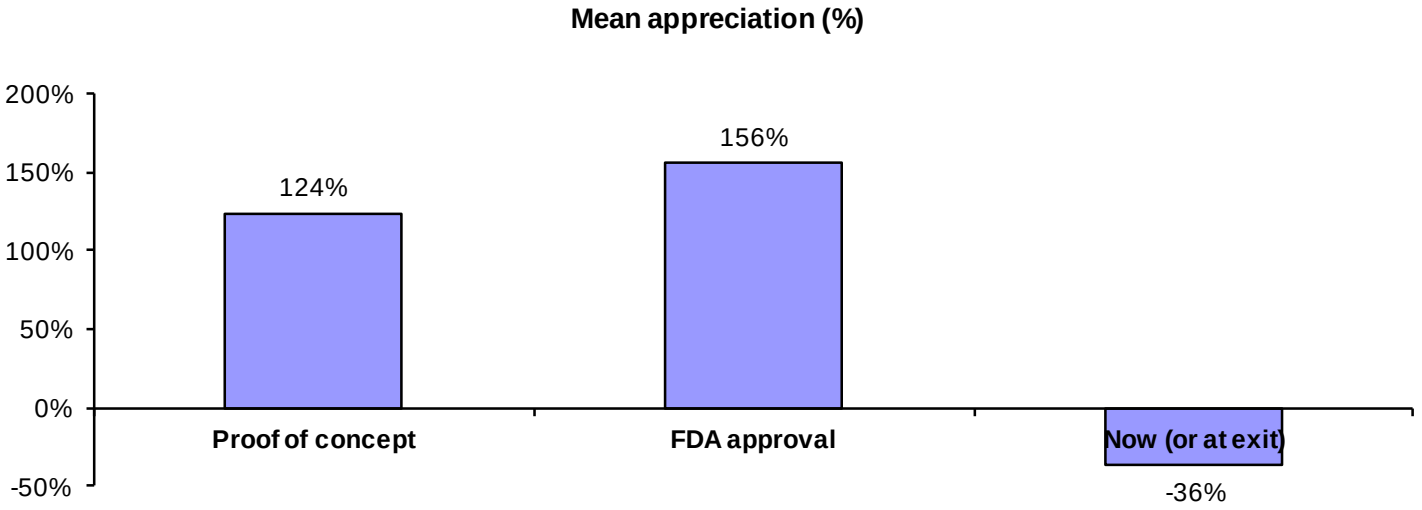
- Study 302 Fails (but not really); Study 301 Succeeds; Study 306a stopped
- FDA advisory committee meeting February 23, 2011
- Current MCAP $232 million

Perceived as an Effective Drug/ Blame the Trials not the Drug?

How is CNS Doing?

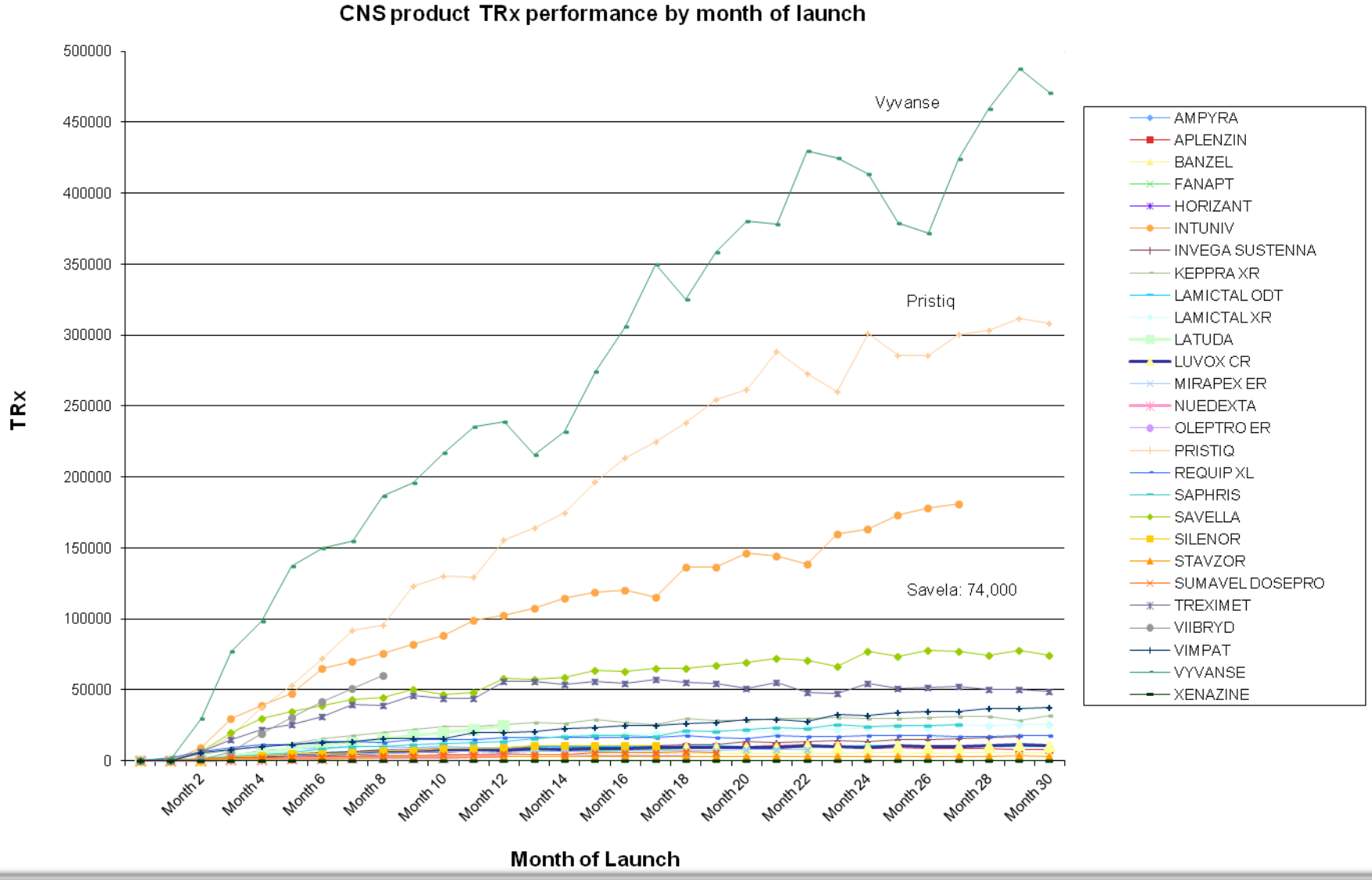
How this reality has translated into value generation to date





Resulting stock price relative to the price at the time of FDA approval is -36%

What the market is telling us



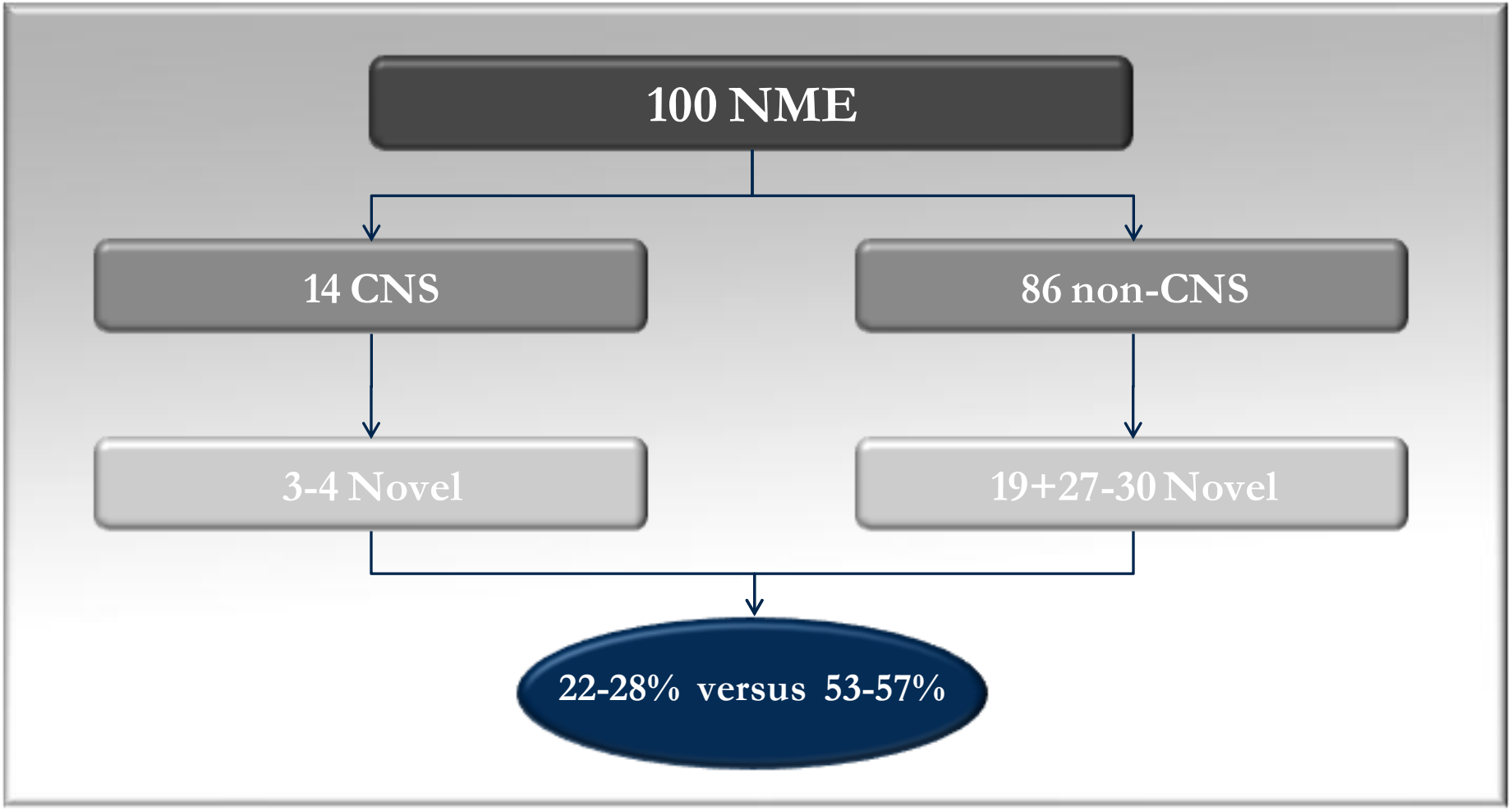
Lacking solid demand – lacking pricing power

The Macro Picture

Why?

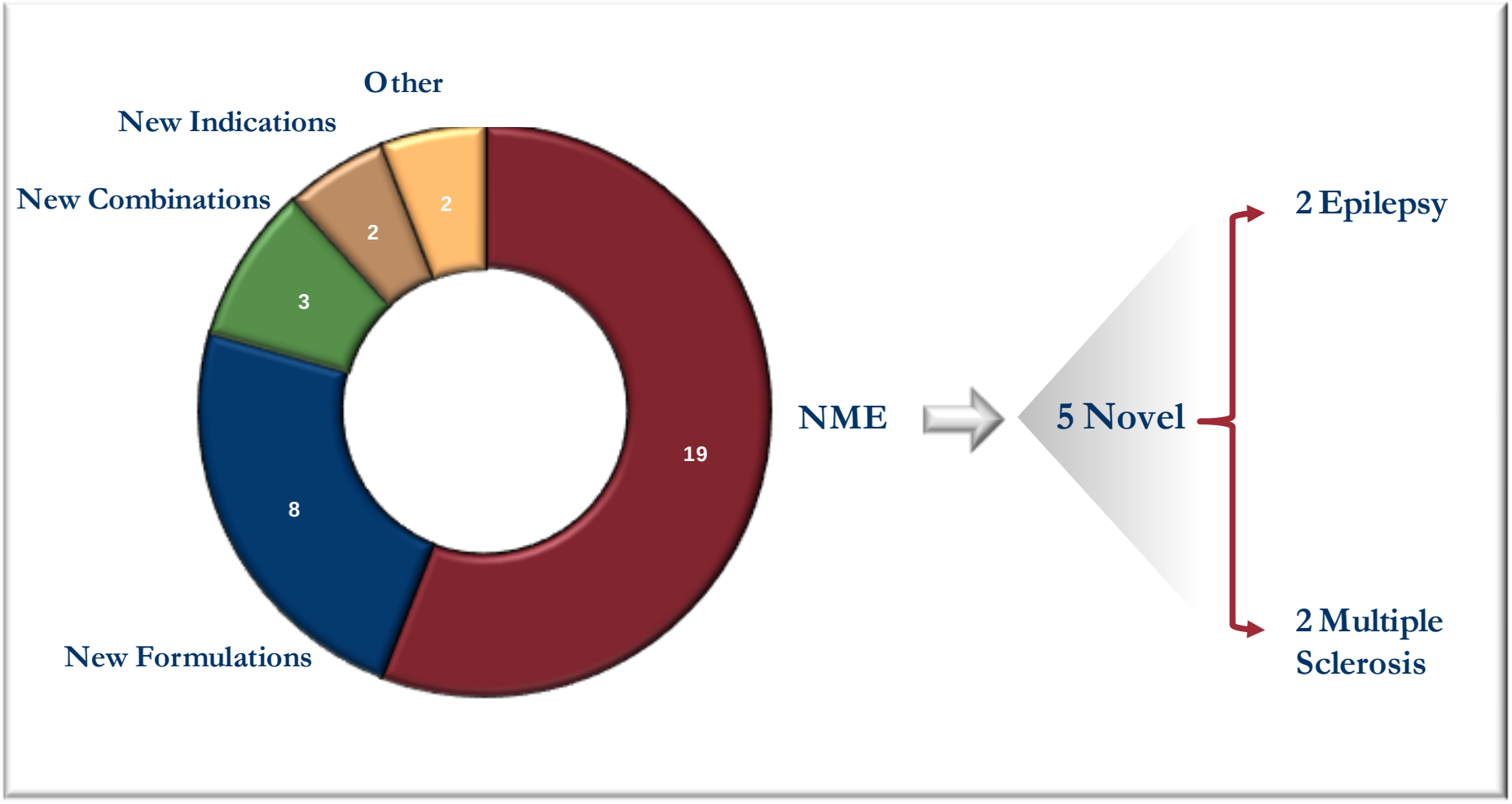
CNS relative performance

FDA Approvals on new molecular entities 08-11



A granular look at CNS approvals

Relevant CNS Approvals 2006-2011



Conclusion

- Wall Street follows you closely
- Wall Street understands a clinically meaningful effect when it sees it
- In many cases CME is difficult to tease out
- For Wall Street, medical necessity is becoming important than clinical meaningfulness in a clinical trial
- This is proving itself out in disappointing revenues and decreasing valuations, the natural outcome of having made investments based on the lowest possible risk
- This downward trend in CNS is unlikely to continue: Wall Street won't continue to fund it

CAVEAT: Catch 22 … give us Biomarkers and narrower indications