Recent impacts on CNS clinical trial recruitment: Qualitative assessment of the impacts & resultant methodological assessment

Michael T. Ropacki

Chief Medical Officer, CNS Clinical Development

Oryzon

President & Principal Scientist

Strategic Global Research & Development

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mropacki@strategicglobalresearch.com

ORYZON

Leader in CNS Epigenetic Therapies

Strategic Global Research & Development

Disclosures

- Full time employee of Oryzon
- Owner and Principal Scientist of SGR&D
- Scientific Advisory Board Member
  - Bon Vivant
  - Neuropathix
  - Neurotrack
  - Novoic
  - Real Sleep
  - ‘Stealth Mode’ SV biopharma

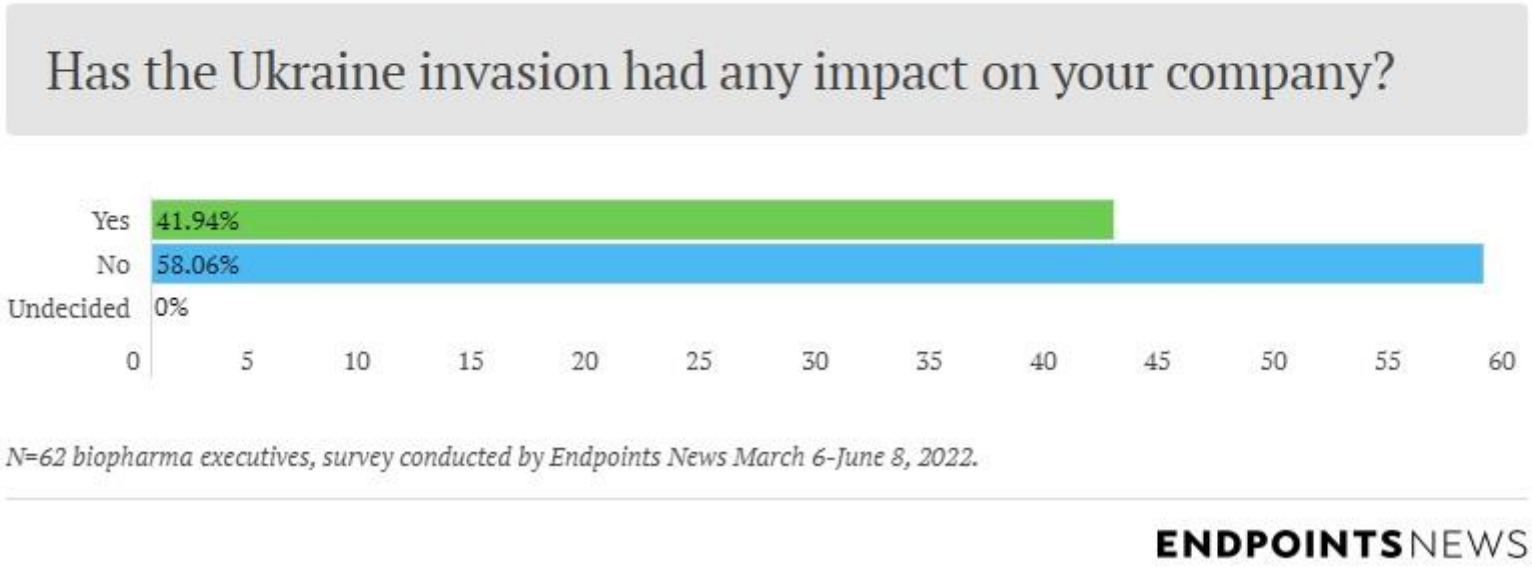
Background

- 18th Annual ISCTM Scientific Meeting – Washington, DC, February 23-25, 2022
  - ➢Podium
    - Leveraging Passive sensing in pharma clinical development
    - Decentralized CNS trials
    - Participant Recruitment & Retention
  - ➢Microphone during Q&As
  - ➢Discussions (Breaks, Lunch, Receptions)
- Personal experience

BIO Survey Results – Global Impact

Q4: The Ukraine invasion hits home

I hadn't actually expected to see such a large concentration of biotechs that have been affected by Russia's Ukraine invasion. It's a minority, but a big minority, and they are feeling the abrupt removal of a large number of clinical research sites from the global network.



N=62 biopharma executives, survey conducted by Endpoints News March 6-June 8, 2022.

ENDPOINTSNEWS

Recent Headlines – Global Impact

May 10, 2022 02:42 PM EDT *Updated 11 hours ago* | R&D, China, Pharma

UPDATED: Scoop: Green Valley's seaweed-derived Alzheimer's drug, approved in China, is halted in PhIII study

Kyle LaHucik
Associate Editor

A Phase III study of a seaweed-derived Alzheimer's drug, conditionally approved in China in November 2019, has been halted, five trial sites have confirmed to *Endpoints News*.

Shanghai-based Green Valley Pharmaceuticals' oligomannate, or GV-971, was in a late-stage Alzheimer's study dubbed "Green Memory," but the trial was halted due to supply chain issues, according to four of the sites. One site said it was not supply chain-related.

Eric Reiman, a former scientific advisor to Green Valley, said he was informed the trial was discontinued "due to unexpected financial challenges related to the COVID-19 Pandemic in China."

Recent Headlines – Global Impact

May 11, 2022 01:09 PM EDT | R&D

Takeda boots a top prospect out of its late-stage pipeline while another is de-layed by war, lockdown

John Carroll
Editor & Founder

Takeda CEO Christophe Weber is putting the last of the debt from the Shire deal to bed now, looking to grow sales from new launches and deal with a drop in profits as its big Vyvanse franchise teeters on the edge of generic competition.

But while the execs today highlighted the plan going forward, the small print in the quarterly review included more troubling setbacks for its pipeline.

TAK-609, one of the top drugs Takeda boasted of from the big Shire buyout, is finally getting the boot after "years of extensive regulatory discussions," the company revealed in their look at fiscal 2021 numbers. According to Takeda:

Recent Headlines – Global Impact

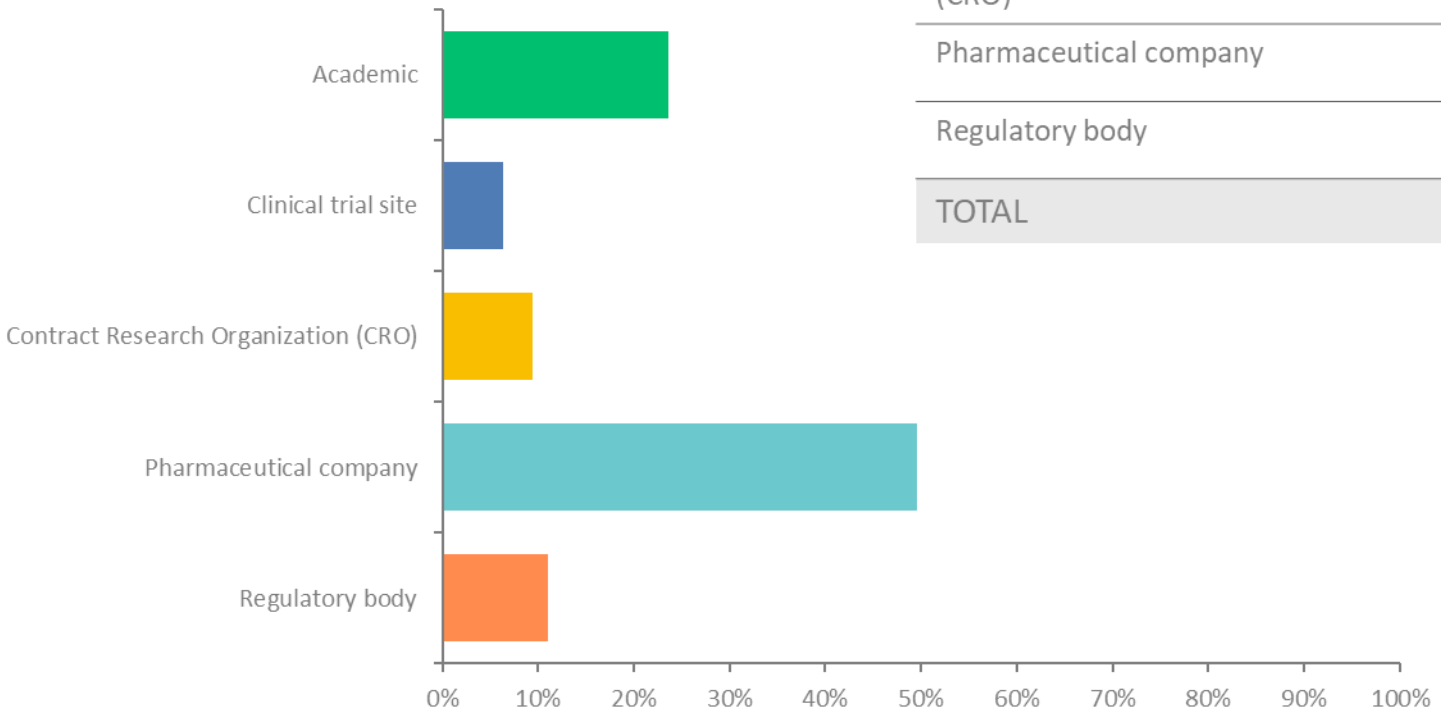
Its partner Ovid, which gained $196 million upfront from Takeda for rights to soticlestat, posted an SEC filing warning that the Ukraine war as well as the China Covid lockdowns are interfering with Takeda's late-stage program — another top contender for the global pharma player.

From the filing:

> *On the afternoon of May 10, 2022, Takeda Pharmaceutical Company Limited ("**Takeda**") notified Ovid Therapeutics Inc. (the "**Company**") that Takeda planned to announce that two pivotal Phase 3 programs evaluating soticlestat for the potential treatment of Dravet and Lennox-Gastaut syndromes are likely to be delayed due to enrollment challenges specifically related to the geopolitical situation in Ukraine and Russia and Covid-19 lockdowns in China. Takeda disclosed it is working on multiple approaches to minimize delays, accelerate recruitment and optimize regulatory timelines for the soticlestat programs. Takeda stated that the studies are actively recruiting patients and remain one of Takeda's highest priority, late-stage, programs. Takeda estimated on its annual earnings call, held on May 11, 2022, that the primary completion date for the soticlestat studies will be March 2024 and anticipates regulatory filings in its fiscal 2024.*

The war in Ukraine has triggered a slate of issues for drug developers, as Big Pharma pulls back from Russia, leaving only essential services in place. The lockdown has also loomed large as a broad range of companies begin to suffer from supply chain glitches.

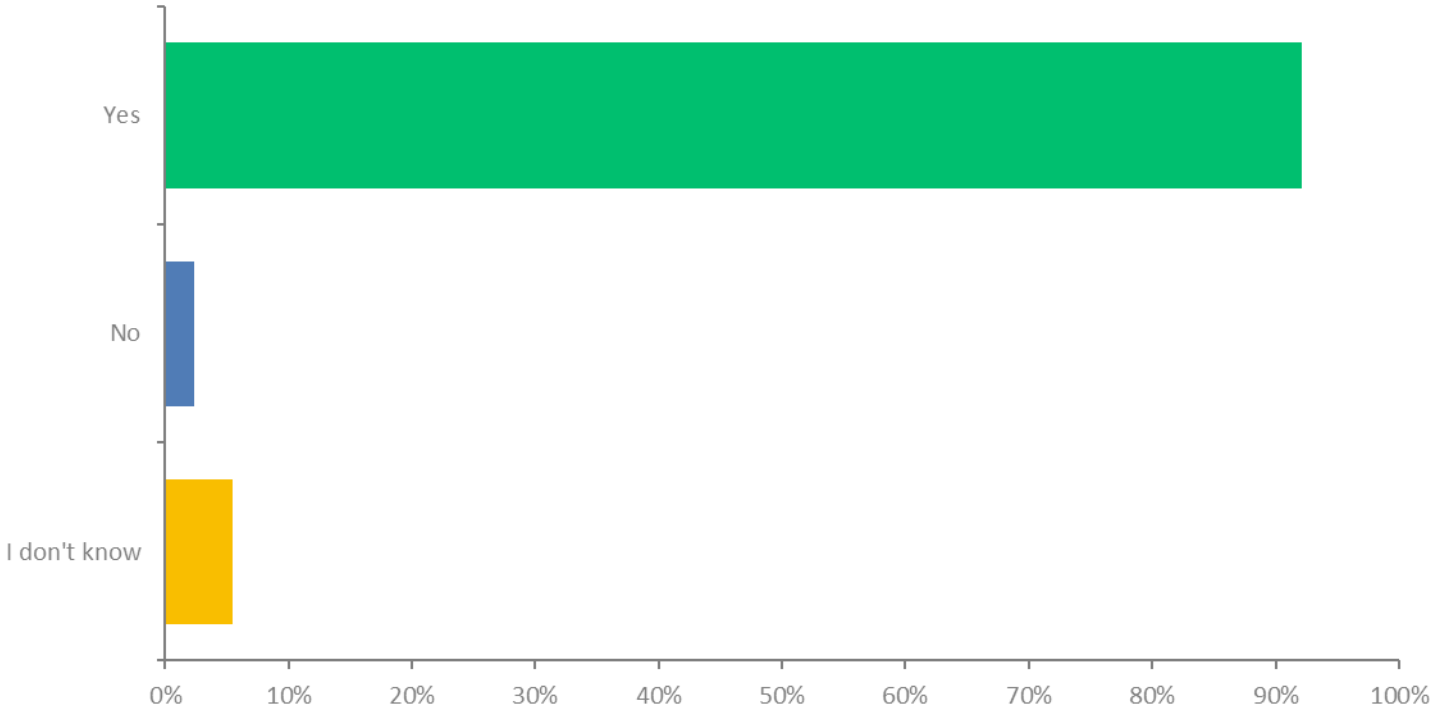
ISCTM Survey: Demographic Breakdown



ANSWER CHOICES	RESPONSES	
Academic	23.62%	30
Clinical trial site	6.30%	8
Contract Research Organization (CRO)	9.45%	12
Pharmaceutical company	49.61%	63
Regulatory body	11.02%	14
TOTAL		127

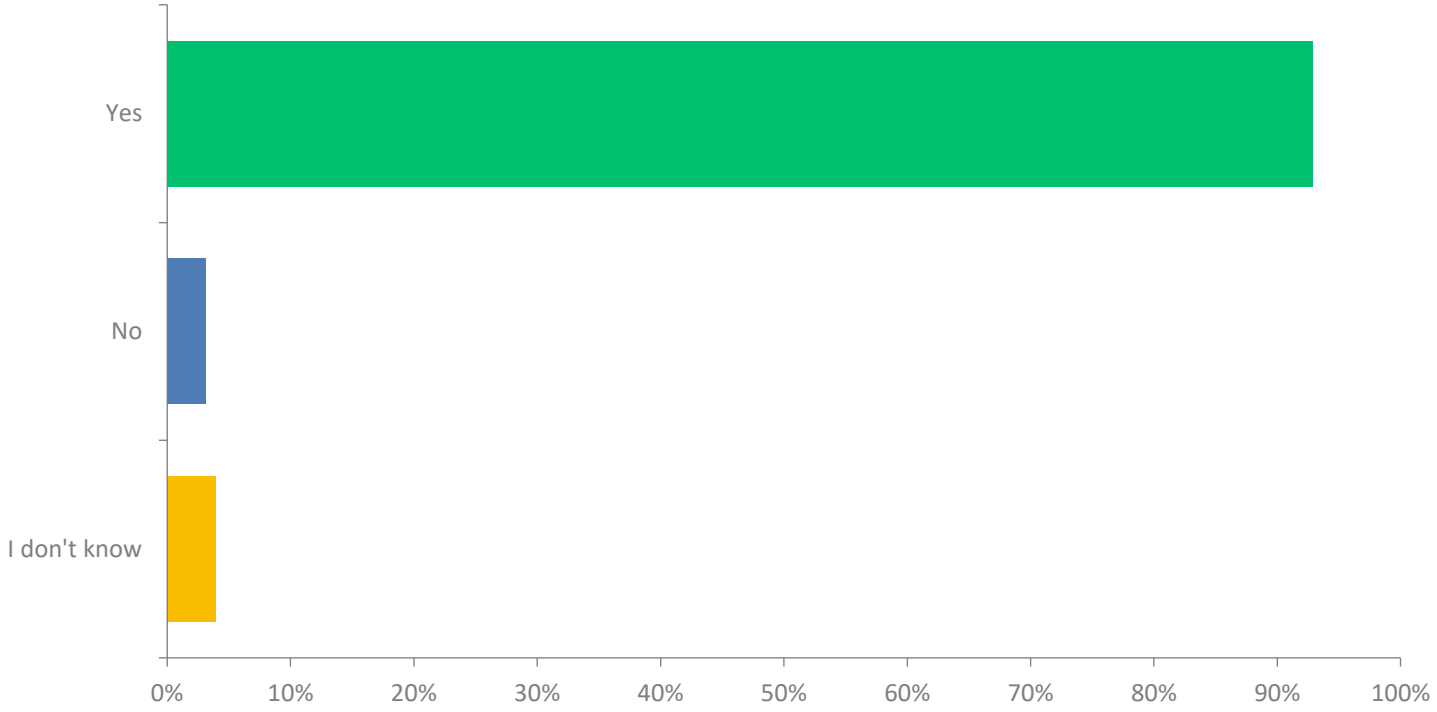
ISCTM Survey: Have recent events complicated execution of CTs?

ANSWER CHOICES	RESPONSES	
Yes	92.13%	117
No	2.36%	3
I don't know	5.51%	7
TOTAL		127



ISCTM Survey: COVID impacted subject recruitment?

ANSWER CHOICES	RESPONSES	
Yes	92.91%	118
No	3.15%	4
I don't know	3.94%	5
TOTAL		127



Site Level Impact:

- BPD RCT initiated March 2020 – not the best time for FPI!
  - ➢ December 2021
    - Site enrollment commitment (Pre-COVID) – approximately 200 subjects
    - Revised enrollment commitment (During COVID) – about 2 dozen
    - Actual randomized subjects – less than 20
- Schizophrenia Negative Symptoms & CIAS RCT began 2H 2021
  - ➢ February 2022
    - Overall enrollment – negligible
- Comparison to Global Data (2000-2022):
    - Depression = 0.25 pps/m
    - Schizophrenia Negative Symptoms = 0.21 pps/m
    - Schizophrenia CIAS = 0.48 pps/m
    - Schizophrenia Negative Symptoms & CIAS = 0.28 pps/m

Methodological Changes

Significantly increased site outreach and touchpoints

- Monthly enrollment updates
  - Including details of how sites are performing in updates
  - Color coding site performance
  - Shutting down non-performing site, that is, after two months of no activity
- Clinical Operations booster calls
- In-person site visits (site tours, lunches/dinners/drinks) & PI interviews
- Educational videos to boost site recruitment – URL and QR Code

Lessons Learned from Site Outreach

- US was not alone in COVID misinformation campaigns
- Patients suffering from psychiatric illnesses are more at-risk to misinformation
  - Negatively impacted BPD trial recruitment
  - Significantly impacted schizophrenia trial recruitment
- COVID had significant negative impact on mental health
  - Stretching an already overworked Psychiatry system
- Manpower shortage is indeed global, especially for Psychiatrists
- Global supply chain issues impacted hospitals/sites
- Research took a backseat to clinical care

Site Level Impact:

- BPD RCT initiated March 2020 – not the best time for FPI!
  - May 2022
    - Overall patients per site/month – approximately 0.4 pps/m
- Schizophrenia Negative Symptoms & CIAS RCT began 2H 2021
  - May 2022
    - Overall enrollment – approximately 0.3 pps/m
- Comparison to Global Data (2000-2022):
    - Depression = 0.25 pps/m
    - Schizophrenia Negative Symptoms = 0.21 pps/m
    - Schizophrenia CIAS = 0.48 pps/m
    - Schizophrenia Negative Symptoms & CIAS = 0.28 pps/m

Conclusions

- Recent world events had a significant and negative impact on global CNS trial recruitment and conduct.
- Trials have become more difficult to conduct.
- Participant enrollment has become increasingly difficult.
- Various unexpected consequences of recent world events
  - Misinformation campaigns
  - Staff shortages
  - Supply chain issues
- Methodological changes, that is, increased site outreach, communications and touchpoints, as well as education can help mitigate negative impact
- Perhaps this higher ‘white glove’ approach should become standard of care

Thank You for your time and attention!

Questions?