AI Support for Mission-critical Pharma Business Decisions

Would AI-based Qinsight™ find key information missed about mongersen?

Abstract
After acquiring the rights to mongersen for $710M, Celgene has terminated a Phase III trial early. Was key information missed about mongersen that would have changed critical business decisions or altered trial design for a greater chance of success? Here we explore the use of AI-based Qinsight in enhancing knowledge discovery and improving critical business decisions.

The Importance of Historical Literature

Historical information from the biomedical literature is central to biopharmaceutical decisions and to the entire $5T healthcare industry. The majority of targets are identified from the literature, and the vast amount of that information provides critical context for decisions at all stages of R&D, as well as for efforts such as medical affairs, publication planning, and more.

Currently, much of the effort to understand the literature relies on old-fashioned search engines, which try to find everything that might possibly be relevant, leaving it to the user to find what they want. This approach is not only time-consuming and frustrating, but more importantly leads to critical information being missed.

Quertle’s Qinsight application uses artificial intelligence to find relevant results right away, as well as AI-driven predictive visual analytics based on the text content itself (vs merely using metadata) to enable intuitive exploration and to support serendipitous discoveries.

Here, we present a case study to provide an example of the power of Qinsight’s advanced discovery methods coupled to its comprehensive content, which covers over 40 million authoritative documents.

Mongersen: A Case Study

Recently, Celgene announced its decision to discontinue a Phase III clinical trial on the use of mongersen to treat Crohn’s disease. Celgene had purchased the rights to mongersen from Nogra Pharma in 2014 for $710M.

With the huge monetary costs as well as opportunity costs involved, we asked if data had been available that could have influenced the decisions leading to this failed trial. The findings presented here are not meant to imply criticism of Celgene, who likely had access to substantial information not available publicly, but to demonstrate how Quertle’s AI-based discovery can be used to enhance current discovery processes and give more confidence to critical decisions.
Background
Mongersen is an antisense oligonucleotide that blocks SMAD7, which is a TGF\(\beta\) type 1 receptor antagonist. Higher levels of SMAD7 have been associated with inflammatory bowel diseases (Boirivant at al.). Hence there was considerable hope that interfering with SMAD7 would be a treatment for Crohn's disease and ulcerative colitis.

Investigative Approach
For this study, we used Qinsight. We applied a Publication Date filter to limit results to information available prior to April 2014 (the point at which Celgene committed to purchasing the rights to mongersen). References provided are representative (out of the over 2000 relevant, pre-April 2014 documents). [Qinsight covers over 44 million authoritative documents, including journal articles, patent literature, treatment protocols, conference abstracts, NIH grants, and more – enabling a comprehensive view within a single interface.] The investigation of historical information took one scientist approximately 1 hour to complete.

The Roles of SMAD7
To understand the potential impacts of altering SMAD7 activity, we used the following queries in Qinsight:

- Which biological processes are connected to SMAD7?
- What diseases are associated with SMAD7?

In addition to the literature expected about the role of SMAD7 in TGF\(\beta\) signaling, there were many documents that demonstrated SMAD7 roles that were TGF\(\beta\)-dependent and roles in a variety of pathologies. For example:

- **Cancer growth and metastasis:** SMAD7 modulates cancer growth and metastasis through TGF\(\beta\)-dependent and independent pathways (e.g., Stolfi et al.; Emori et al.; DeVito et al.; Zhu et al.) with both positive and negative roles being described. The mongersen trials appear to have excluded patients with a history of cancer.

- **Liver function:** SMAD7 plays an important role in liver function and its loss increases apoptosis of hepatocytes (e.g., Zhu et al.; Halder et al.).

- **Wound healing:** SMAD7 promotes wound healing (e.g., Wang; Hori et al.), hence its downregulation may adversely affect this process.

- **Fibrosis:** Loss of SMAD7 contributes to fibrosis in kidneys, lungs, peritoneum, and liver (see Zhu et al., for example).

*These findings suggest downregulation of SMAD7 could have adverse effects outside the expected therapeutic goal. In the case of mongersen in the clinical trials, note that enteric-coated oral delivery should minimize affects outside the lower gastrointestinal tract. However, given the role of SMAD7 in wound healing, we (as non-experts in this field) wonder if IBD lesions would heal more slowly.*
**Regulation of SMAD7**

We next investigated the regulation of SMAD7 to gain insights into possible feedback mechanisms that might compensate any inhibition of SMAD7 by mongersen. To understand the regulation of SMAD7 activity, we used the following queries in Qinsight:

- Which genes regulate SMAD7?
- microRNAs regulate SMAD7
- lncRNAs regulate SMAD7

SMAD7 expression is induced by TGFβ1, providing feedback directly in the well-known TGFβ pathway (blocking SMAD7 allows TGF-β1 to work better in reducing inflammation, but SMAD7 is induced by TGF-β1 – creating a feedback loop (Stopa et al.). In addition, there are several other layers of control by regulatory proteins including TIEG (TGFβ inducible early gene), which downregulates SMAD7. Several other proteins (including STRAP, YAP65, KLF10, and AIP4) influence SMAD7 through recruitment. Degradation of SMAD7 is mediated by E3 ubiquitin ligases such as Smurf2 (Moore et al.) and Cbl-b (Gruber et al.).

This complex regulation of SMAD7 goes well beyond protein-modulated effects and includes several regulatory RNAs as well. For example, microRNA miR-21 (Zhao et al.) and miR-181a (Parikh et al.) repress SMAD7. [More recent literature shows substantial involvement of long non-coding RNAs such as HOTAIR and XIST.]

> The complexity of SMAD7 regulation suggests that any decrease in SMAD7 expression due to mongersen might unexpectedly be modulated by intersecting pathways.

**Trial Design**

In investigating the regulation of SMAD7, one additional query used in Qinsight was:

- What chemicals regulate SMAD7?

followed by queries for specific compounds such as,

- statin and SMAD7

In those results, several compounds were identified. Of particular interest were the articles connecting statins to SMAD7 expression. Kim et al. reported simvastatin inhibited the induction of SMAD7 in mice. In contrast, simvastatin upregulated SMAD7 in pigs (Chade et al.) and fluvastatin increased SMAD7 expression in a rat model (Zhai et al.). We are unaware if statin use was identified as a patient subpopulation in the mongersen clinical trials.

Mongersen delivery is administered orally with a pH-dependent metacrylic acid polymer coat (Monteleone et al.). Hence, in Qinsight we queried:

- affects intestinal pH
- $chemicals decrease colon pH
- $chemicals decrease ileum pH

(note: $chemicals is one of many Qinsight shortcuts for getting results with actual compounds without cluttering the results with hits that contain generic terms such as “chemical”, “compound”, etc.)
The most relevant results from these investigations related to the intestinal microbiome, especially lactic acid-producing organisms (e.g., Ranganathan). In addition, both prebiotics (Flesch et al.) and probiotics (Nilsson and Nyman) influence intestinal pH. Hence, prebiotics or probiotics taken by trial participants may influence functional dosage of mongersen. Although antibiotics were not allowed before study entry or during the trials, probiotic use could be an important non-regulated variable. In addition, dietary choices (fiber, oligosaccharides) can decrease colon pH (Neyrinck et al.). Some substances, such as aldosterone, can increase distal colon pH (Maguire et al.).

There may have been opportunities to select specific sub-populations to improve the clinical trial outcomes. Controlling for statin use and/or dietary influences on the gut microbiome may have identified responder classes, thus enhancing the personalized medicine opportunities.

Conclusions
The results from this short analysis confirmed the opportunity (down-regulating SMAD7 using mongersen to treat IBD), but also identified several potential red flags and trial design considerations. These discoveries from the historical literature can be used to

- prioritize and focus early research,
- improve design of clinical trials,
- identify additional applications for treatments being studied,
- help position the product in the literature,
- better understand the competitive landscape,
- and much more

With about 88% of candidate drugs entering clinical trials failing to gain regulatory agency approval, the types of insights demonstrated here for mongersen could prove to be critical for all pharmaceutical endeavors. Qinsight's AI-based discovery with predictive visual analytics can be incorporated at all stages. A single insight missed by your current approaches might even save you $710M (or make that investment pay off).

Also consider the time savings in getting to the critical literature fast. For a patented therapy going through development, being able to find the relevant information 30 days sooner can save $83M in revenue for a drug that becomes a $1B/year earner.

"I found in just a few minutes what previously took months!"

– KK Wong, Professor at MD Anderson, Industry Consultant

FOR MORE INFORMATION: If you are interested in what Qinsight can do for your mission-critical decisions, contact Quertle at info@quertle.com.