

## Sirtuins and ghrelins in the spotlight with Novartis-Elixir deal



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Novartis' recent option deal with Elixir Pharmaceuticals to acquire the private US biotech or license Elixir's oral ghrelin antagonist programme followed a decision by the Swiss pharma giant to drop its rights to another two of Elixir's pre-clinical programs, sirtuins and ghrelin agonists ([EP Vantage Interview - Elixir patiently waiting for Novartis takeout, June 8, 2009](#)).

A review of pipeline data from EvaluatePharma for these novel classes of drug, that act on the sirtuin and ghrelin pathways with the potential to treat a wide range of disorders, not only provides an insight into why Novartis opted for the ghrelin antagonist. It also highlights some of the companies operating in this fledgling field that could be receiving renewed interest from other big pharma partners (see tables below).

### **Ghrelin agonists to the fore**

The table below illustrates that the most advanced candidates which act on ghrelin, a naturally occurring hormone involved in stimulating appetite and food consumption, are all agonists designed to help treat wasting disorders like cachexia in patients suffering from cancer, COPD or AIDS.

| Ghrelin pathway products: pipeline |                      |                      |                        |  |  |
|------------------------------------|----------------------|----------------------|------------------------|--|--|
| Phase                              | Pharma Class         | Product              | Company                | Originator   | Indication Summary   |
| Phase II                           | Ghrelin agonist      | Ipamorelin           | Helsinn Healthcare     | Novo Nordisk   | Post-operative ileus (POI) [Phase II]  |
|                                    | Ghrelin agonist      | Anamorelin (RC-1291) | Helsinn Healthcare     | Novo Nordisk   | Cachexia (wasting) [Phase II]  |
|                                    | Ghrelin agonist      | SUN 11031            | Daiichi Sankyo         | Asubio Pharma  | Cachexia (wasting) [Phase II]; Anorexia nervosa [Phase II]   |
|                                    | Ghrelin agonist      | TZP-101              | Tranzyme Pharma        | Tranzyme Pharma  | Post-operative ileus (POI) [Phase II]; Gastroparesis [Phase II]; Cachexia (wasting) [Pre-clinical] |
|                                    | Ghrelin agonist      | TZP-102              | Tranzyme Pharma        | Tranzyme Pharma  | Gastroparesis [Phase II]; Gastro-oesophageal reflux disease (GORD/GERD) [Pre-clinical]             |
|                                    | Ghrelin agonist      | GTP-300              | Rose Pharma            | Rose Pharma  | Cachexia (wasting) [Phase II]  |
|                                    | Ghrelin agonist      | GTP-200              | Rose Pharma            | Rose Pharma  | Cachexia (wasting) [Phase II]; Other metabolic indications [Phase I]                               |
|                                    |                      |                      |                        |  |  |
| Pre-clinical                       | Ghrelin agonist      | BIM 28131            | Ipsen                  | Ipsen  | Cachexia (wasting) [Pre-clinical]  |
|                                    | Ghrelin agonist      | EX-1314              | Elixir Pharmaceuticals | Bristol-Myers Squibb                                   | Cachexia (wasting) [Pre-clinical]; Gastroparesis [Pre-clinical]                                    |
|                                    | Ghrelin agonist      | ST-1141 (RC-1141)    | Helsinn Healthcare     | Sapphire Therapeutics                                  | Constipation, opioid-induced [Pre-clinical]  |
|                                    | Ghrelin agonist      | GTP3XX               | Rose Pharma            | Rose Pharma  | Other metabolic indications [Pre-clinical]   |
|                                    | Ghrelin agonist      | AZP-01               | Alizé Pharma           | Alizé Pharma   | Diabetes, type II (maturity onset) [Pre-clinical]  |
|                                    | Ghrelin antagonist   | Ghrelin Antagonist   | Elixir Pharmaceuticals | Elixir Pharmaceuticals                                 | Diabetes, type II (maturity onset) [Pre-clinical]; Obesity [Pre-clinical]                          |
|                                    | Ghrelin antagonist   | Ghrelin Antagonist   | Helsinn Healthcare     | Novo Nordisk   | Obesity [Pre-clinical]   |
|                                    | Ghrelin antagonist   | Ghrelin Antagonists  | Æterna Zentaris        | Zentaris/University of Milan/University of Montpellier | Obesity [Pre-clinical]   |
|                                    | Anti-ghrelin aptamer | NOX-B11              | NOXXON Pharma          | NOXXON Pharma  | Obesity [Pre-clinical]   |
|                                    | Anti-ghrelin vaccine | CYT014-T2Qb          | Cytos Biotechnology    | Cytos Biotechnology                                    | Obesity [Pre-clinical]   |
|                                    |                      |                      |                        |  |  |
| Research project                   | Ghrelin antagonist   | TZP-301              | Tranzyme Pharma        | Tranzyme Pharma  | Obesity [Research project]   |

With seven agonist candidates in phase II, but only in the hands of five small to medium size companies, this suggests the field remains fairly narrow and has yet to attract the interest of big pharma.

Meanwhile the development of ghrelin antagonists, which have the potential to suppress appetite and increase insulin sensitivity, remains at a much earlier stage with just four candidates at the pre-clinical or research project phase.

Helsinn Healthcare's recent acquisition of Sapphire Therapeutics, which held probably the most comprehensive portfolio of ghrelin agonists and antagonists, indicates that the ghrelin field is generating some interesting activity as companies jostle for position. The likes of Tranzyme Pharma and Rose Pharma, private US and Danish companies respectively, could therefore be receiving some new and renewed interest in their programmes since Novartis made its move on Elixir.

### Glaxo ring-fenced sirtuins

The field of sirtuins received high profile exposure last year when GlaxoSmithKline paid \$720m to acquire Sirtris Pharmaceuticals, one of the few companies developing a clinical stage pipeline of products which interact with these enzymes which regulate multiple metabolic pathways.

The table below reveals that Glaxo is now way ahead of the developmental competition for sirtuin-related products.

Aside from Glaxo and Elixir, only MethylGene and Santhera Pharmaceuticals have any research ongoing in this novel area, which has the potential to treat a wide range of disorders from diabetes to cancer to Huntington's disease.

Therefore, with Elixir's sirtuin and ghrelin agonist pre-clinical programs some way behind the developmental competition, Novartis' decision to go for Elixir's ghrelin antagonist program instead looks like a wise one on the basis that this candidate represents the best chance of being first-in-class.

| Sirtuin pathway products: pipeline |                           |                         |                        |  |  |
|------------------------------------|---------------------------|-------------------------|------------------------|--|--|
| Phase                              | Pharma Class              | Product                 | Company                | Originator   | Indication Summary   |
| Phase II                           | Sirtuin (SIRT1) activator | 184072                  | GlaxoSmithKline        | GlaxoSmithKline  | Diabetes, type II (maturity onset); Colorectal cancer; General blood malignancies              |
| Phase I                            | Sirtuin (SIRT1) activator | 2245840                 | GlaxoSmithKline        | GlaxoSmithKline  | Diabetes, type II (maturity onset); COAD/COPD  |
| Pre-clinical                       | Sirtuin (SIRT1) modulator | SIRT1 Modulator Program | GlaxoSmithKline        | Sirtris Pharmaceuticals  | Diabetes, type II (maturity onset); General cancer indications; General inflammatory disorders |
|                                    | Sirtuin (SIRT1) inhibitor | SIRT1 Inhibitor         | Elixir Pharmaceuticals | University of California/Massachusetts Institute of Technology | Huntington's disease; General cancer indications   |
|                                    | Sirtuin (SIRT2) inhibitor | SIRT2 Inhibitor         | Elixir Pharmaceuticals | University of California/Massachusetts Institute of Technology | Diabetes, type II (maturity onset); Obesity  |
|                                    | Sirtuin (SIRT1) activator | SIRT1 Activator         | Elixir Pharmaceuticals | University of California/Massachusetts Institute of Technology | Diabetes, type II (maturity onset); Obesity  |
| Research project                   | Sirtuin (SIRT2) modulator | SIRT2 Modulator Program | GlaxoSmithKline        | Sirtris Pharmaceuticals  | General cancer indications [Research project]; Other neurological indications                  |

|  | Modulator                 | Program                     |                          |                          | Neurological Indications [Research project]   |
|--|---------------------------|-----------------------------|--------------------------|--------------------------|---|
|  | Sirtuin (SIRT3) modulator | SIRT3 Modulator Program     | GlaxoSmithKline          | Sirtris Pharmaceuticals  | Other metabolic indications [Research project]; General cardiovascular indications [Research project] |
|  | Sirtuin (SIRT4) modulator | SIRT4 Modulator Program     | GlaxoSmithKline          | Sirtris Pharmaceuticals  | Other metabolic indications [Research project]; General cardiovascular indications [Research project] |
|  | Sirtuin (SIRT5) modulator | SIRT5 Modulator Program     | GlaxoSmithKline          | Sirtris Pharmaceuticals  | Other metabolic indications [Research project]  |
|  | Sirtuin (SIRT6) modulator | SIRT6 Modulator Program     | GlaxoSmithKline          | Sirtris Pharmaceuticals  | General cancer indications [Research project]   |
|  | Sirtuin (SIRT7) modulator | SIRT7 Modulator Program     | GlaxoSmithKline          | Sirtris Pharmaceuticals  | Other metabolic indications [Research project]  |
|  | Sirtuin inhibitor         | Sirtuin inhibitor program   | MethylGene               | MethylGene               | General cancer indications [Research project]   |
|  | Sirtuin modulator         | SIRT deacetylase-modulators | Santhera Pharmaceuticals | Santhera Pharmaceuticals | Other musculoskeletal disorders [Research project]  |