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Odanacatib’s 15 minutes of fame

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The past two years have been busy ones in the world of biopharmaceutical development, so you might be excused if during this time you had completely forgotten about Merck & Co’s novel oral osteoporosis project odanacatib.

For a brief moment in 2013 this cathepsin K inhibitor had featured as Merck’s most valuable R&D asset, but after completing phase III it fell into a black hole amid lingering doubts over its safety. Those doubts proved to have been well founded when on Friday Merck broke the radio silence to announce that odanacatib was being ditched.

The reason for the discontinuation was the project's association with an increased risk of stroke. This was determined by an independent analysis of major cardiovascular events after a pivotal fracture outcomes study had shown a numerical imbalance in adjudicated stroke events, Merck said.

It was cardiovascular events that, along with somewhat limited efficacy, had rudely interrupted the sellside’s brief infatuation with odanacatib (*Long-awaited Loft data justify sellside’s odanacatib caution, September 16, 2014*).

With the possible increased risk of atrial fibrillation, death and the skin condition morphea, as well as stroke, the 16,713-patient Loft study reduced the project’s possible benefit to once-weekly oral dosing and the avoidance of osteonecrosis of the jaw. Merck delayed filing, and then as immuno-oncology took centre stage the sellside virtually forgot about odanacatib.

Cathepsin K

The idea behind odanacatib was that, by inhibiting the osteoclast enzyme cathepsin K, bone resorption could be reduced and the course of osteoporosis slowed.

There are many different cathepsin types. Jazz’s Defitelio, marketed for hepatic veno-occlusive disease, a life-threatening complication of haematopoietic stem cell transplantation, is a cathepsin G inhibitor, while Roche’s cathepsin S inhibitor RG7625 is in phase II trials as an immunosuppressant.

Numerous cathepsin K inhibitors have been studied for treating osteoporosis and osteoarthritis, and odanacatib is not the first to fall by the wayside. The casualties include Novartis’s balicatib – discontinued owing to skin reactions including morphea – and Glaxo’s relacatib.

Cathepsin K inhibitors			
Project	**Company**	**Status**	**Trial ID**
MIV-711	Medivir	Phase II	NCT02705625
AM-3701	Amura Holdings	Preclinical	–
Odanacatib	Merck & Co	Abandoned in phase III	NCT00529373
ONO-5334	Ono Pharmaceutical	Abandoned in phase II	NCT00532337
Balicatib/AAE581	Novartis	Abandoned in phase II	NCT00371670
Relacatib/GSK462795	GlaxoSmithKline	Abandoned in phase I	NCT00411190
MIV-701 & MIV-710	Medivir	Abandoned in phase I	–
NC-2300	Nippon Chemiphar	Abandoned in phase I	–
VEL-0230	Velcura Therapeutics	Abandoned in phase I	–
Org 219517	Schering-Plough	Abandoned in preclinical	–

With odanacatib's discontinuation the only active cathepsin K-targeting agents still in development are Medivir's MIV-711 and Amura Holdings' AM-3701, according to *EvaluatePharma*.

Though Medivir's main focus is clearly hepatitis B, a phase II trial of MIV-711 accounts for much of its R&D spending; the study is to read out in the second half of next year. Amura, a private UK biotech focused on various cathepsin inhibitors, has not generated any news since 2012, and has yet to move a project into the clinic.

With the cathepsin K inhibitor class now tainted with toxicity it might be that Medivir and Amura have to rethink their plans. The demise of odanacatib will also boost Amgen, which in the antibody romosozumab has a filed osteoporosis MAb with an unobstructed shot at approval.

There was a time when such an outcome would have greatly bothered Merck, but that was before it developed Keytruda.

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