

Drug makers leave the pain behind



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Developing non-opioid analgesics remains one of the hardest tasks in biopharma.

August is a time for relaxing, holidaymaking and, apparently, culling unpromising pain projects. This month no fewer than five groups gave up on mid or late-stage agents for various intractable pain conditions, and this included one of the few big pharmas in this space, Lilly.

Despite the huge underserved need that guarantees rich rewards for any group that can bring a successful novel painkiller to market, a search for new therapies entering the clinic yields precious little.

The most recent pain candidate to crash out of development was Aptinyx's NMDA modulator NYX-2925. The agent had lurched from [failure](#) to [failure](#), but the company only shifted away from it after the miss in a phase 2b fibromyalgia trial. Even then the group said it would "continue to analyse the data", even as it refocused on its other products.

In the weeks before, Eliem, Acadia and Ampio had also admitted defeat with their putative painkillers. Ampio had taken its TLR 7 agonist all the way through phase 3, but in April the FDA told it that its most recent phase 3 trial was inadequate. Investors might wonder why it took the cash-strapped, penny-stock company this long to pull the plug, and indeed some have filed lawsuits alleging mismanagement.

Pain projects: what's gone...

Project	Company	Mechanism	Status
Phase 3			
Ampion	Ampio	TLR 7 agonist	Abandoned Aug 3 following failure of most recent ph3 osteoarthritis trial
Phase 2			
LY3016859	Lilly	TGF alpha & epiregulin MAb	Dropped from pipeline in Q1 ; no explanation
ACP-044	Acadia	Redox modulator	Abandoned Aug 8 based on data from a previous ph2 bunionectomy study
ETX-810	Eliem	Prodrug of palmitoylethanolamide	Abandoned Aug 2 following failure of ph2a lumbosacral radicular pain trial
NYX-2925	Aptinyx	NMDA modulator	Abandoned Aug 12 following failure of ph2b fibromyalgia trial
<i>Source: Evaluate Pharma, clinicaltrials.gov & company statements.</i>			

At least some groups have managed to keep going. South Korea's Vivozeon stated at the end of May that two phase 3 studies of VVZ-149, one in the US in post-bunionectomy patients and one in its home country in colorectal resection, were ongoing. No reporting date has been given.

And last month Vertex laid out pivotal plans for VX-548. Two phase 3 studies in moderate to severe acute pain following bunionectomy or abdominoplasty surgery are to start at by the end of the year, comparing the sodium channel blocker with hydrocodone bitartrate plus acetaminophen. A single-arm phase 3 in multiple other types of moderate to severe acute pain is also on the slate, as is a phase 2 in neuropathic pain.

Two in, one out

Three big pharmas are still plugging away in phase 2. Lilly quietly dropped one of its candidates, LY3016859, earlier this year, but expects mid-stage data on its TRPA 1 inhibitor LY3526318 in osteoarthritis, diabetic peripheral neuropathic pain (DPNP) and low back pain in the coming months.

The SSTR4 agonist LY3556050 remains listed in its pipeline, but a phase 2 trial in DPNP was terminated last month, according to clinicaltrials.gov. It will be interesting to see if this project remains in development when Lilly reports third-quarter results.

Entirely new entrants into this nightmarishly difficult space are thin on the ground. The private Swiss biotech Novaremed is one of the few brave enough to set foot here with a pain therapy that is neither an opioid nor a reformulation of a long-established analgesic. It plans to take its NMDA receptor antagonist into a mid-stage study next year, and another project is to reach phase 2 sooner, albeit in an academic trial.

The effort to develop novel painkillers beyond opioid therapy is laudable, but this is undeniably one of the riskiest gambles drug development has to offer. The sad fact is that, for all the companies in the table below, failure is far more likely than success.

... and what's still going

Project	Company	Mechanism	Status
Phase 3			
Fasinumab	Teva/ Regeneron	Anti-NGF MAb	Update on plans awaited
VER-01	Vertanical	Cannabis extract	Ph3 ongoing (in Germany only) in chronic lower back pain; ct.gov record has not been updated since Sep 2021
VVZ-149	Vivozon	5-HT _{2A} receptor antagonist; GlyT2 inhibitor; PX2 purinoceptor 3 antagonist	Ph3 trials in postoperative pain ongoing in S Korea and the US
Phase 2			
VX-548	Vertex	Nav1.8 sodium channel blocker	Ph3 in acute pain and ph2 in neuropathic pain to start in Q4 2022
BIIB074 (vixotrigine)	Biogen	Nav1.7 sodium channel blocker	2 ph3 trials in trigeminal neuralgia, Surge-1 and Surge-2 , registered with late 2022/early 2023 start dates
LY3526318	Lilly	TRPA 1 antagonist	Data from 3 ph2 trials, in OA , DPNP and low back pain , could emerge in 2022
LY3556050	Lilly	SSTR4 agonist	Ph2 in DPNP terminated in Jul 2022 on slow enrolment; plans unclear
MEDI7352	Astrazeneca	Anti-NGF/TNF bispecific MAb	Data due in 2023 from 2 ph2 trials in DPNP and OA
BAY2395840	Bayer	Bradykinin B1 receptor antagonist	Ph2 in diabetic nerve pain started this year
GRC 17536	Glenmark	TRPA 1 antagonist	Ph2b in DPNP with preserved small nerve fibre function said to have been planned for Q2 2022 but has not begun
OLP-1002	Olipass	Nav1.7 sodium channel 9a antisense	Small ph2 in OA ongoing (Australia only)
Phase 1			
NRD.E1/ NRD135S.E1	Novaremed	TYK regulator	Eppic-Net , investigator-sponsored ph2 trial in DPNP, to begin 2022
MP-101	Novaremed	NMDA receptor antagonist	Ph2 trial in chemotherapy-induced neuropathy and neuropathic pain to begin Q1 2023
GSK3858279	GSK	CCL17 inhibitor	Ph1 in OA ongoing (Australia only)
ST-2427	Siteone Therapeutics	Nav1.7 sodium channel blocker	Ph1 in healthy volunteers ongoing; agent is intended for chronic, acute and ocular pain
Trichomylin	Zyus Life Sciences/ Novotech	Cannabinoid agonist	Hope, ph1 in OA , ongoing (Australia only)

DPNP=diabetic peripheral neuropathic pain. OA=osteoarthritis. Excludes gene and cell therapies. Source: Evaluate Pharma, clinicaltrials.gov & company statements. Phase 1 projects were selected based on a novel mechanism and an ongoing, active trial that was started in the last two years.

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