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Poor industry scorecard drives desmoteplase rescue plan

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Analysts had written off the stroke project desmoteplase after its failure in the phase III Dias-3 trial in June, but you can hardly blame its owner, Lundbeck, for trying to find a way forward.

As the barrage of statistics released for today's World Stroke Day attests, stroke is a hugely unmet need, but the industry's success rate in developing treatments is lamentable (see table). While desmoteplase's second pivotal study, Dias-4, is likely also to fail, the move to re-analyse Dias-3 presents an intriguing opportunity to tilt it in the right direction.

Lundbeck could, for instance, amend the Dias-4 design before the data are unblinded and released next year. Since its re-analysis of Dias-3 suggests that MRI is more accurate than CT scanning at detecting ischaemic injury in stroke patients outside the three-hour window, it could seek to limit the primary analysis of Dias-4 – prospectively – to only those patients who had been assessed by MRI.

Of course, a major issue is that the patient population will likely be too small to see a significant effect, especially as Dias-4 recruitment had been halted prematurely as a result of the failure of Dias-3.

As such, any move to alter the way Dias-4 is analysed would at best be persuasive. Lundbeck said it was too early to comment on any plans, and further development – in any case not expected before next year – would be subject to guidance from "key clinical and regulatory experts during the next few months".

The advice could well be to plough on; there is only one drug approved for treating acute ischaemic stroke – Roche's alteplase – and this must be given within three hours of stroke symptom onset. The goal behind the similarly acting desmoteplase was to demonstrate efficacy between three and nine hours after onset.

Beyond desmoteplase the industry pipeline targeting this setting is meagre, and the Lundbeck project is its only phase III asset, *EvaluatePharma* shows. The mid-stage industry pipeline tends to focus on treating the longer-term effects of stroke damage rather than targeting the acute phase.

Thus several cell therapy approaches for post-stroke rehabilitation are being investigated, including SanBio's SB623 and ReNeuron's ReN001. Meanwhile, the recent track record paints a sorry picture.

Selected failures in acue ischaemic stroke

Project	Company	Note
Desmoteplase	Lundbeck	Failed Dias-3, first of two pivotal trials. Dias-4 data due in 2015.
DP-b99	D-Pharm	Abandoned after phase III study was halted for futility.
Microplasmin	Thrombogenics	Abandoned in stroke. Marketed as Jetrea for vitreomacular traction.
GSK737004 (S-0139)	GSK/Shionogi	Abandoned in phase II.
AX200	Sygnis Pharma	Failed 350-patient phase II Axis-2 study. Abandoned.
V10153	Vernalis	Abandoned in phase II.

Dias-3 had recruited 492 patients but failed to show a difference in functional scores between desmoteplase and placebo (*Desmoteplase fail vindicates Paion's exit, June 30, 2014*). But Lundbeck recently revealed that CT might have incorrectly detected ischaemic brain injury, confounding the study protocol.

In fact only 284 patients were found to have met Dias-3's recruitment criteria, and if only these are considered a treatment effect favouring desmoteplase can be seen, Lundbeck insists.

If Lundbeck's contention that MRI is the way to screen these patients to ensure a more accurate diagnosis

holds water, the company might be able to squeeze out a positive read-out of sorts from Dias-4. But it still faces a huge clinical practice hurdle: “Today most stroke patients are evaluated with a CT scan,” it says.

After the failure of Dias-3 Credit Suisse cut its probability of desmoteplase reaching the market from 15% to 5%. At best Lundbeck might hope for a strong enough signal to run a better-designed pivotal programme, and the fact that the analysts still expect blockbuster sales in five years – if it is successful – surely suggests that desmoteplase is worth pursuing, up to a point.

On the other hand Dias-4 could fail to show any benefit at all on any of the measures explored in Dias-3. Such an outcome would scupper the Danish firm’s MRI theory and send it right back to square one.

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