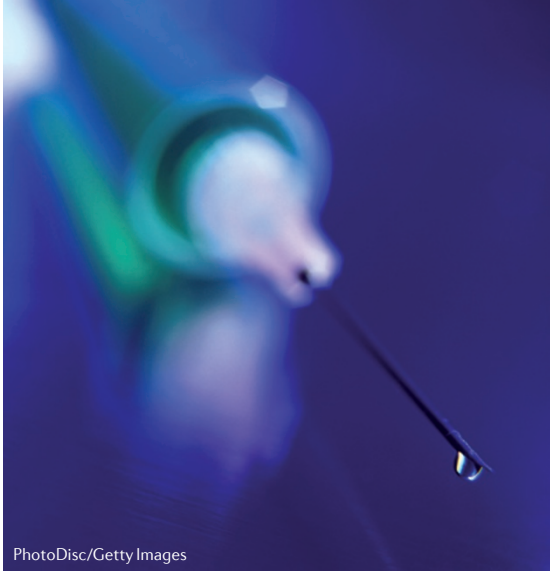
REGULATORY WATCH

Antisense approval provides boost to the field



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Mipomersen (Kynamro; Isis Pharmaceuticals/Genzyme), a second-generation antisense oligonucleotide that inhibits apolipoprotein B100, was approved in January by the US Food and Drug Administration (FDA) for homozygous familial hypercholesterolaemia (HoFH), a rare genetic disorder that leads to excessive levels of low-density lipoprotein (LDL) cholesterol.

Although mipomersen is not the first antisense therapy to reach the market — fomivirsen was approved by the FDA in 1998 for cytomegalovirus retinitis in patients with AIDS, but later discontinued owing to reduced need of the therapeutic — its approval was highly anticipated as a potential validation of the scientific and commercial promise of antisense as a platform technology.

"The approval of mipomersen shows that a second-generation antisense drug given systemically for a chronic disease in which safety is paramount can be developed and approved," says Stanley Crooke, founder and CEO of Isis. "It confirms that the technology we have created could be used to develop drugs for other types of indications such as cancer and inflammatory diseases."

For patients with HoFH, mipomersen provides another new treatment option, following the FDA approval in December 2012 of lomitapide (Juxtapid; Aegerion) — a small-molecule inhibitor of microsomal triglyceride transfer protein. "The current standard of care for these patients is weekly or bi-weekly LDL apheresis, an invasive procedure that physically removes LDL particles from the bloodstream," says Robert Hegele, Director of the Blackburn Cardiovascular Genetics Laboratory at the University of Western Ontario, Canada. It is hoped that the direct suppression of apolipoprotein B synthesis — and therefore LDL particles — by mipomersen will enable patients to reach target LDL levels more efficiently while reducing the frequency of LDL apheresis, he adds.

Given mipomersen's side effects (most notably hepatic toxicity) — which were the main reason why, last year, the European Medicines Agency turned down its initial application for approval there — the FDA has required a risk evaluation and mitigation strategy (REMS) and post-marketing studies to evaluate its safety (lomitapide's approval also came with similar requirements).

Whatever the ultimate place of mipomersen in the treatment of patients with hypercholesterolaemia, Crooke's view is that the time and investment taken to reach this point — 23 years and about US$3 billion — compares favourably with that for monoclonal antibodies. "The creation and validation of the potential breadth of monoclonal antibodies took about 30 years and I think perhaps as much as $30 billion," he says. And as the field matures, third-generation antisense approaches are emerging that could further establish the technology as a platform. "There are several new approaches to the use of antisense molecules, or molecules that act like antisense, that will continue to be explored with vigour, such as morpholino and locked oligonucleotides and EGS [external guide sequence]-based technology," says Sidney Altman, Yale University, Connecticut, USA. In the meantime, results from other antisense therapies in late-stage clinical trials (TABLE 1) are keenly anticipated.

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Table 1 | **Selected antisense therapies that have reached Phase III trials***

Drug (developer)	Target and mechanism of action	Indications	Trial name (estimated completion date)
Aganirsen (Gene Signal)	*IRS1* inhibitor	Corneal neovascularization	I-GRAFT (April 2013)
Belagenpumatucel-L (NovaRx)	*TGFB2* inhibitor	Non-small-cell lung cancer	STOP (June 2013)
Drisapersen (GlaxoSmithKline/Prosensa Therapeutics)	*DMD* modulator	Duchenne muscular dystrophy	DMD114044 (July 2013)
Custirsen (OncoGenex Pharmaceuticals)	*CLU* inhibitor	Castration-resistant prostate cancer and non-small-cell lung cancer	SYNERGY (December 2013)
DIMS-0150/Kappaproct (InDex Pharmaceuticals)	*NFKB1* inhibitor and TLR9 modulator	Refractory ulcerative colitis	COLLECT (March 2014)
Trabedersen (Antisense Pharma)	*TNFSF13* inhibitor and TGFβR2 antagonist	Refractory or recurrent anaplastic astrocytoma	SAPPHIRE (halted owing to slow patient recruitment)
Alicaforsen (Atlantic Healthcare)	*ICAM1* inhibitor	Ulcerative colitis and pouchitis	Unknown

CLU, clusterin gene; *DMD*, dystrophin gene; *ICAM1*, intercellular adhesion molecule 1 gene; *IRS1*, insulin receptor substrate 1; *NFKB1*, nuclear factor-κB1 gene; *TGFB2*, transforming growth factor β2 gene; TGFβR2, TGFβ receptor 2; TLR9, Toll-like receptor 9; *TNFSF13*, tumour necrosis factor ligand superfamily member 13 gene. *Data from Cortellis database (Thomson Reuters), BioMedTracker (Sagient Research) and ClinicalTrials.gov website.