Medicines & Healthcare products Regulatory Agency

What is the landscape for licensing of genomic therapies (MHRA)

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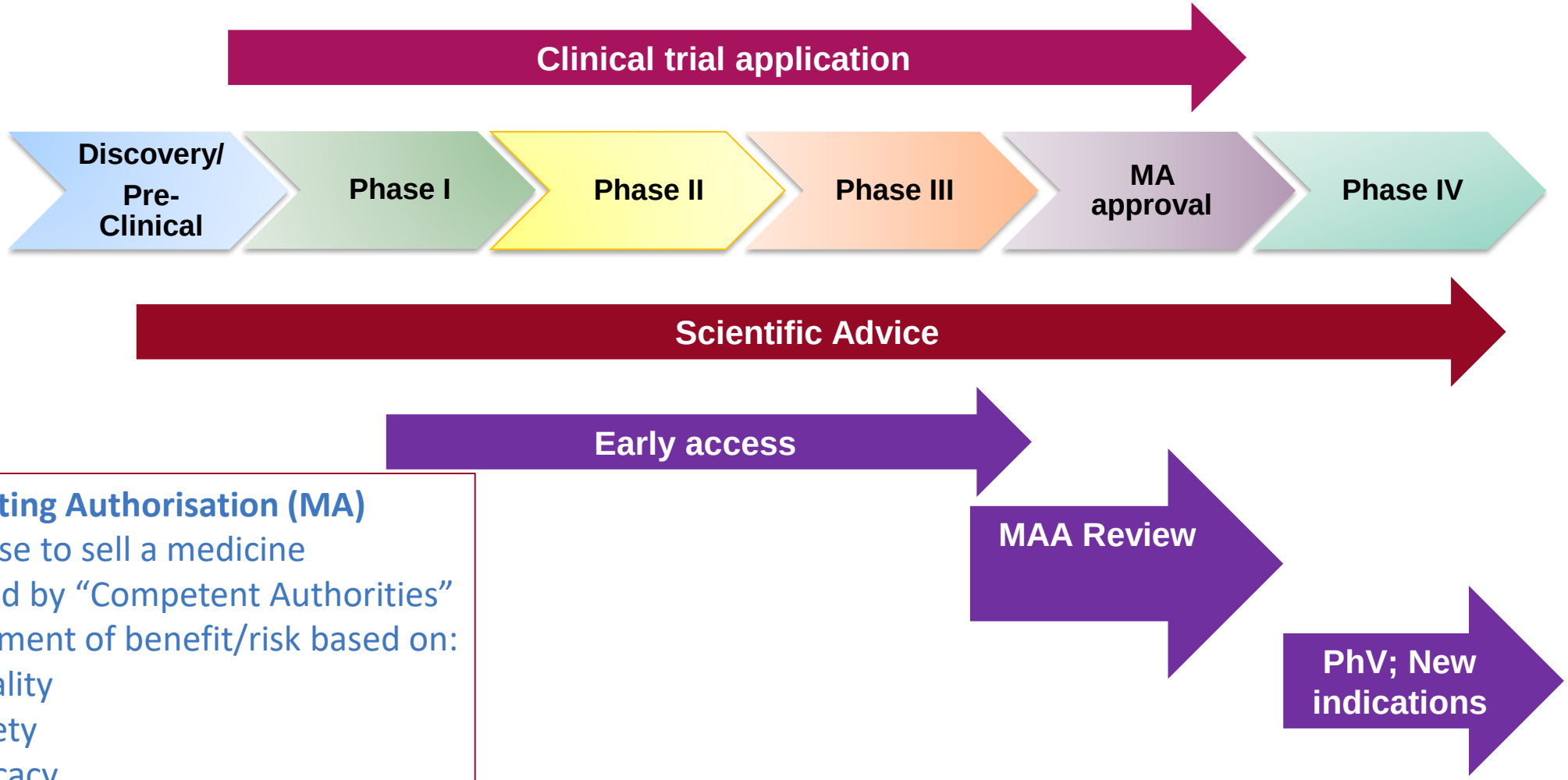
Disclaimer

No financial interests to declare

The opinions expressed are those of the speaker and do not necessarily reflect the official position of any affiliated organization, group or committee

Regulatory aspects



Marketing Authorisation (MA)

A license to sell a medicine

Granted by "Competent Authorities"

Assessment of benefit/risk based on:

- Quality
- Safety
- Efficacy

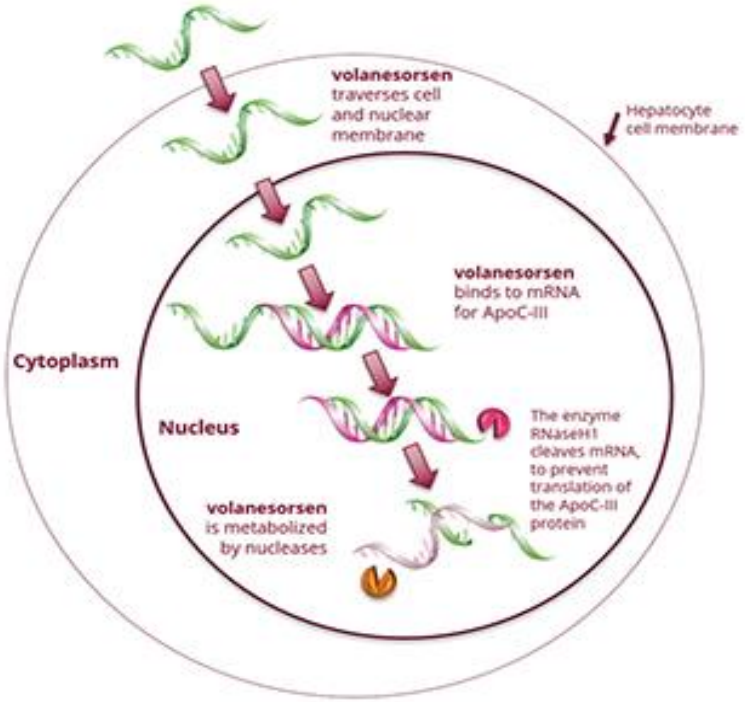
Regulatory pathway

- ***Scientific Advice meeting***
  - Clinical trial application
  - Quality – Non clinical – Clinical development plan
- ***Clinical Trial authorisation application***
- ***Innovative Licensing and Access Pathway (ILAP)***
  - MHRA/NICE/AWTTC/SMC supported by NHS England-NHS improvement/HRA/NIHR
  - Innovation passport (IP)
  - Target Development Profile (TDP)
- ***(Early Access to Medicines scheme ; EAMS)***
- ***Marketing Authorisation application***
  - National / EC Decision Reliance Procedure / ACCESS consortium / Project ORBIS
  - Advanced therapy medicinal products (ATMPs)
  - Full marketing authorisation – Conditional – Exceptional circumstances / Orphan
- ***Pharmacovigilance /Post-Marketing obligations***

Volanesorsen (Waylivra)

Volanesorsen

- Volanesorsen (ISIS 304801, ISIS-ApoCIIIRx) is a 2′-O-2-methoxyethyl (2′-MOE) antisense oligonucleotide (ASO) targeting apoC-III
- selectively binds within the 3′ untranslated region (at base position 489–508) of apoCIII mRNA
- prevents the translation of the apoCIII mRNA and allows ribonuclease H1-mediated mRNA degradation, promoting TG clearance through LPL-independent pathways



Familial chylomicronaemia syndrome (FCS):

Rare (orphan), genetic disorder of lipid metabolism caused by mutations in the lipoprotein lipase (LPL) gene

- **Prevalence**: 1-2/million; est. 3000-5000 pts globally; est.130 patients in the UK-known 89 patients managed within the lipid clinic network
- **Characterised** by very high levels of TGs in the plasma and a build-up of chylomicrons
- **Symptoms**: abdominal pain, fatigue, impaired cognition, numbness or tingling sensation
- **Morbidities/complications:** unpredictable and recurrent acute pancreatitis, (60-80%) of patients; chronic pancreatitis; pancreatic necrosis; fatty liver disease; diabetes; poor QoL
- ***Very limited therapeutic options***

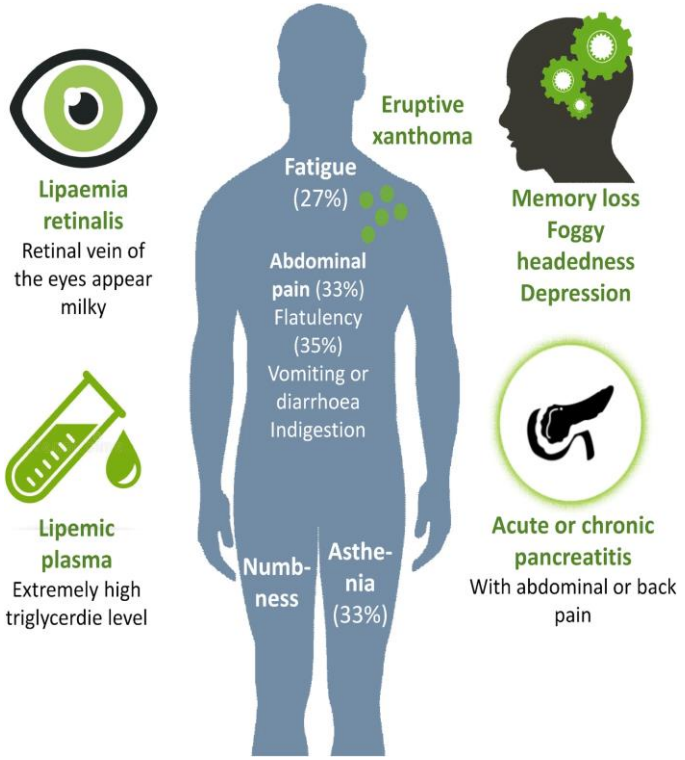
Volanesorsen (Waylivra)

- **APPROACH (CS6 pivotal trial)**

❑ Randomised double-blind placebo controlled trial in 66 FCS pts:

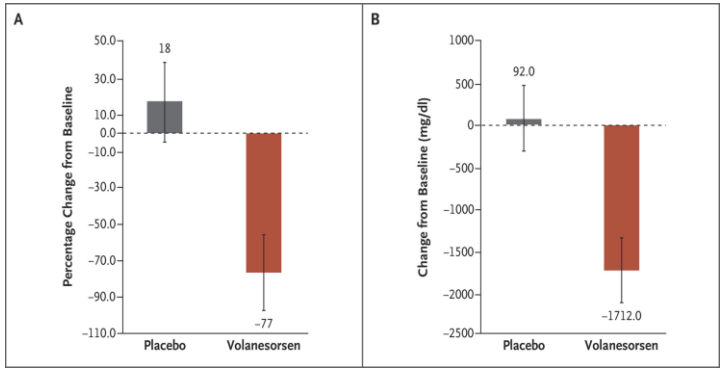
- Adults with history of chylomicronemia
- A diagnosis of FCS (Type 1 hyperlipoproteinemia) with at least one of the following:
  a) Confirmed homozygote, compound heterozygote, or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, APOC2, GPIHBP1, or LMF1)
  b) Post heparin plasma LPL activity of≤20% of normal
- Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at screening.
- History of pancreatitis

❑ Randomised to subcutaneous 285 mg volanesorsen or placebo as a single 1.5 ml injection, once weekly for Weeks 1 to 52



Volanesorsen (Waylivra)

TG analysis	Statistic	Placebo (N = 33)	Volanesorsen (N = 33)
	N	33	33
Baseline (mg/dL)	Mean (SD)	2152 (1153)	2267 (1259)
Month 3 (mg/dL)	Mean (SD)	2367 (1315)	590 (497)
% Change from Baseline	LS Mean (95% CI)	17.6 (-4.0, 39.2)	-76.5 (-97.4, -55.5)
Treatment Comparison of % Change vs Placebo			
Relative Difference in % Change		-94.1	
95% CI		(-121.7, -66.6)	
p-value		<0.0001	



Pancreatitis	Placebo (N=33)		Volanesorsen (N=33)	
Overall Incidence	Patients	Events	Patients	Events
Events During Study	3	4	1	1
p-value	p = NS			
Patients at High Risk	Patients	Events	Patients	Events
Patients with multiple previous events (5 yrs)	4	17	7	24
Events During Study	3	4	0	0
p-value	p = 0.02			

Volanesorsen (Waylivra)

- Thrombocytopenia

	Placebo (N = 33) n (%)	Volanesorsen (N = 33) n (%)	All Patients (N = 66) n (%)
Patients with baseline platelet counts	33	32	65
Number (%) patients with confirmed nadir platelet count < 140,000/mm^3	8 (24.2)	24 (75.0)	32 (49.2)
Number (%) patients with confirmed nadir platelet count < 100,000/mm^3	0 (0.0)	15 (46.9)	15 (23.1)
Confirmed Nadir Platelet Count Post-Baseline			
100,000/mm^3 to < 140,000/mm^3	8 (24.2)	9 (28.1)	17 (26.2)
75,000 to < 100,000/mm^3	0 (0.0)	6 (18.8)	6 (9.2)
50,000 to < 75,000/mm^3	0 (0.0)	6 (18.8)	6 (9.2)
25,000 to < 50,000/mm^3	0 (0.0)	1 (3.1)	1 (1.5)
0 to < 25,000/mm^3	0 (0.0)	2 (6.3)	2 (3.1)

- Injection site reactions: ~80% of patients; mostly mild

- Immunogenicity: ~ 33% of volanesorsen-treated pts tested positive for anti-drug antibodies; no major impact on safety-efficacy

Volanesorsen (Waylivra)

- **Feb 2014**: Orphan designation - EMA
- **July 2017**: Marketing Authorisation Application - EMA
- **June 2018**: Ad Hoc Expert Advisory group - EMA
- ***June 2018: Early Access (EAMS) granted by MHRA***
- ***Aug 2018: Refused by FDA***
- ***Sep 2018****: LPLD Alliance letter to CHMP*
- ***Feb 2019: Positive opinion by CHMP***
  - *Conditional approval - Additional obligations*
- ***Sep 2020: Approved by UK NICE*** *(available to NHS with a discount)*

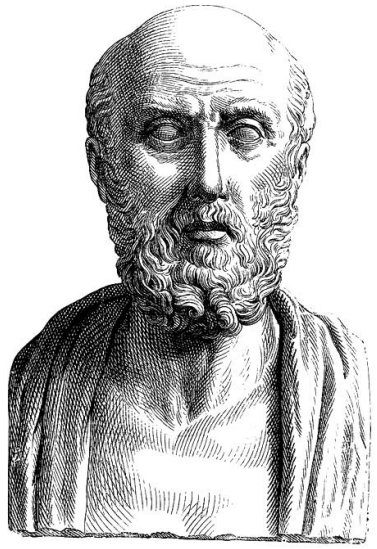
Indication:
Waylivra is indicated as an adjunct to diet in adult patients with **genetically confirmed** familial chylomicronemia syndrome (FCS) and **at high risk for pancreatitis**, in whom response to diet and triglyceride lowering therapy has been inadequate

➢ **Close platelet monitoring / dose adjustment protocol / discontinuation rules**

Summary/issues

- **Technology /novel therapeutic target**
- **Rare genetic, seriously debilitating condition**
- **Limited ther. options / high unmet need**
- **Small population**
  - Surrogate efficacy measures
  - Small safety database
- **Indication of high efficacy BUT**
  - Uncertain long term compliance and clinical benefit
- **Safety concerns**
- **Divergent regulatory views**
- ***Input from patients – experts***
- **Overall positive benefit:risk subject to additional measures (conditional MA)**

Ὁ βίος βραχύς, ἡ δὲ τέχνη μακρή, ὁ δὲ καιρὸς ὀξύς,
ἡ δὲ πεῖρα σφαλερή, ἡ δὲ κρίσις χαλεπή



Life is short and art (medicine) long, opportunity fleeting, experience treacherous, and judgment difficult.

Hippocrates

Thank you