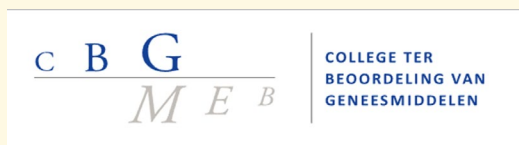




Central Committee on Research Involving Human Subjects

Dutch Competent Trial Authority and Central Ethics Committee

Drug Registrations



Trial Registrations (including CTR, MDR, IVDR)



Part I
(Competent Authority)

Part II
(Ethics Committee)

One committee meeting
-ATMP's
-nontherapeutic studies
in minors/incapacitated
One Scientific/
Regulatory Advice



*CCMO supervises 11
accredited Ethics Committees
for drug trial evaluations*

	ASO ('..rsen')		siRNA ('...siran')		other*	
Number of Studies	82		38		9	
Rejections	5	(6%)	1	(2%)	-	-
Number of Compounds	49		16		6	
Development Stopped/Uncertain	21	(41%)	1	(6%)	1	(17%)
Development Ongoing	22	(47%)	10	(63%)	5	(83%)
Registration Pending/Completed (EMA/ FDA) <i>(italics: no studies in NL)</i>	4	(9%)	5	(31%)	-	-
	nusinersen (SMA-1) volansorsen (FHC) <i>inotersen (TTA-P/C)</i> <i>fomivirsen (CMV retinitis)</i>		givosiran (porphyria) inclisiran (FHC) lumasiran (PH-1) vutrisiran (TTA-P/C) patisiran (TTA-P/C)			
	5 mipomersen (FHT) viltolarsen (DMD) casimersen/golodirsen eteplirsen (DMD) <i>tofersen (SOD1-ALS)</i>					

* splicing modifiers, small activating RNA, coding mRNA

Classified as public by the European Medicines Agency

Common Grounds for Deliberation and Questions (and sometimes rejection)

- rejection rates:

 - ASO's: 6% of studies (+9% withdrawals during evaluation)

 - siRNA's: 2% of studies (+4% withdrawals during evaluation)

- major rejection grounds:

 - insufficient supportive evidence (pharmacological/pharmacokinetic)

- unfavorable risk/benefit balance (non-therapeutic studies in children):

 - ASO's: 35% studies in minors (5% exclusively in children <12 years)

 - siRNA's: 26% studies in minors (4% exclusively in children <12 years)

Recommendations to Facilitate Trial Approval

- scientific advice (CCMO plus CBG/MERB):
 - academic groups!
 - new approaches (but also share in prior experience)
- provide strong pharmacological rationale:
 - pharmacokinetics (tissue penetration)
 - pharmacodynamics (RNA transcripts / protein levels)
 - selectivity
- consistently incorporate biomarkers to guide dose selection (from FIM)!
- in children: avoid studies limited to 'pharmacokinetics/tolerability/safety'
 - 'seamless' phase I/IIa in pediatric patients