-Central Committee on Reseach Involving Human Subjects

Dutch Competent Trial Authority and Central Ethics Committee

Drug Registrations

CBG MEB
COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

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*) *(italics: no studies in NL)*	4 nusinersen (SMA-1) volansorsen (FHC) *inotersen (TTA-P/C)* *fomivirsen (CMV retinitis)* 5 mipomersen (FHT) viltolarsen (DMD) casimersen/golodirsen eteplirsen (DMD) *tofersen (SOD1-ALS)*	(9%)	5 givosiran (porphyria) inclisiran (FHC) lumasiran (PH-1) vutrisiran (TTA-P/C) patisiran (TTA-P/C)	(31%)	-	-

* splicing modifiers, small activating RNA, coding mRNA

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