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Regulatory perspective on Single Arm Trials and the implications for the benefits and risks

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Context

Key to regulatory decision making = Benefit/Risk balance

- Sufficient evidence of efficacy and safety of the product should be submitted
- RCT the golden standard but if justified, evidence can be obtained from a SAT.

→ EMA Reflection paper on establishing efficacy based on singlearm trials submitted as pivotal evidence in a marketing authorisation application (9 September 2024).

Single arm trials

SATs lack the following key design features:

- a concurrent control arm,
- randomised allocation to treatment,
- enrolment of subjects without knowledge of their subsequent assignment,
- and blinding of participants, investigators and outcome assessors to treatment assignment.

→ Uncertainties and bias!

SAT weakness: lack of an internal control

- Difficult to interpret treatment effect
  - what would have happened under no treatment?
- Difficult to characterize safety profile
  - are the AEs related to treatment or disease?
- External validity may be difficult to determine
  - uncertainty of treatment effect size and/or safety profile in clinical practice

Possibility: the patient is its own control

Methodological considerations

For a successful SAT, the following considerations apply:

- a priori definition of a clear success criterion
- Adherence to trial protocol (no unplanned change is the post hoc designation of a trial planned as exploratory trial (e.g. phase II) to a pivotal trial once trial data were available)
- Choice of PEP:
  - objectively measurable
  - able to isolate treatment effects
  - time-to-event endpoints are usually not suitable in SATs to isolate a treatment effect

Methodological considerations

Choice of target and trial population:

- very important in SAT
- determines the plausibility of assumptions about the disease course in the hypothetical control group (counterfactual)
- interpretation of results is more challenging in settings with high patient or disease heterogeneity

External control group

Partial solution: External Control Group

- External control group should be pre-defined in the protocol
- Possible options
  - Patients observed at the same time
  - Historical controls
  - Estimation from literature is considered as realistic value

Acceptability of external control

- Are the populations comparable?
  - in- and exclusion criteria, stage or severity of disease
  - baseline characteristics (matching)
  - treatment history or concomitant medications
  - time periods, standard of care
  - centre related differences
- Are all known prognostic factors measured in both groups?
- Is the primary endpoint measured the same way?
- Are Adverse Events recorded?

Always unknown factors in which they will differ!

Acceptability of external control

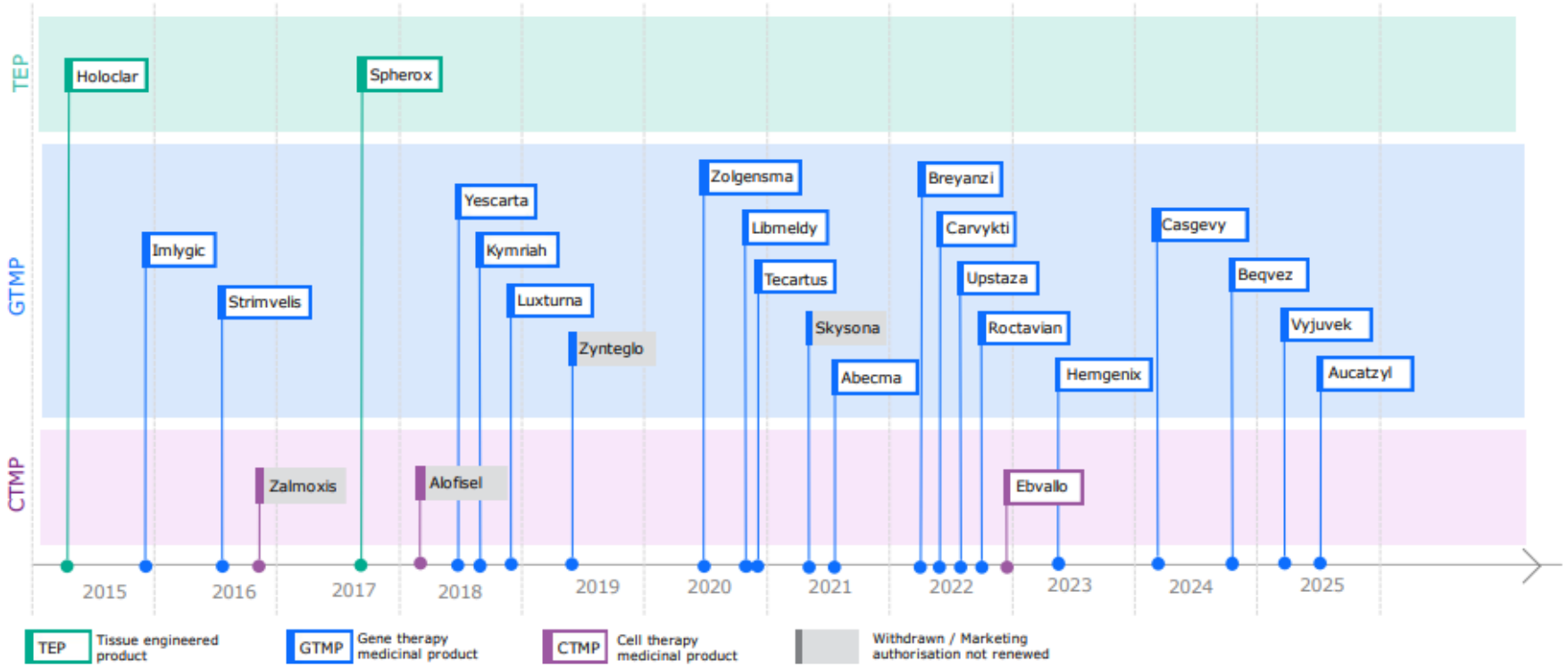
External control group is only useful if:
(ICH E10 guideline)

- A large treatment effect is expected
- Natural disease course is highly predictable
- Endpoint is objective

New EMA reflection paper on external controls currently being drafted

SAT in the field of ATMPs

The last 10 years of ATMPs



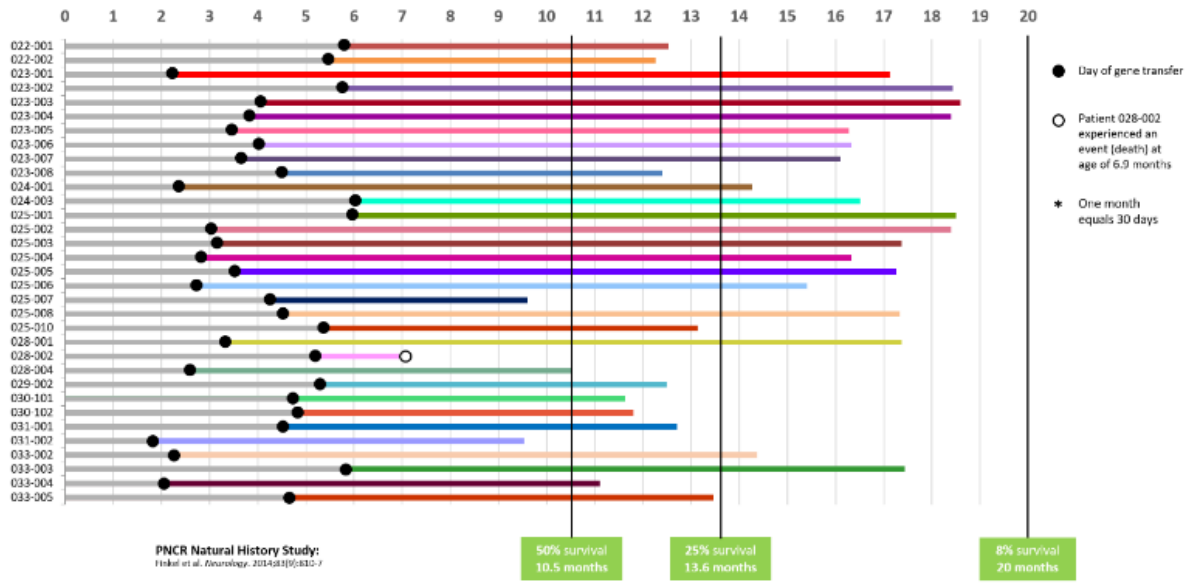
Advanced therapy medicinal products

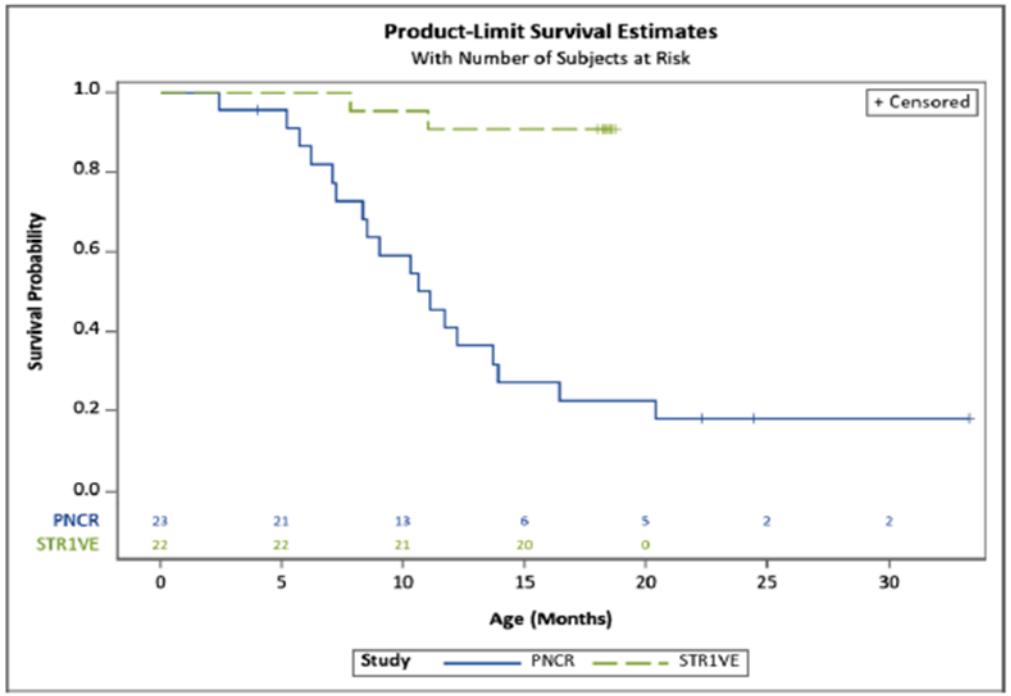
EMA

	Indication	pivotal trial	endpoint	External control?	type of MA
Zolgensma	SMA	SAT	Co-primary of motor milestones and survival	yes (supportive)	CMA
Libmeldy	metachromatic leukodystrophy	SAT	Co-primary The total GMFM and ARSA activity (PBMC and CSF) score two years after treatment	yes (supportive)	full MA
Tecartus	relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy	SAT	Overall Response Rate (ORR)	yes (supportive)	CMA
Skysona	early cerebral adrenoleukodystrophy	SAT	Proportion of subjects who were alive and have none of the 6 major functional disabilities (MFDs) at Month 24 Visit (i.e. Month 24 MFD-free survival).	yes (supportive)	full MA
Abecma	relapsed and refractory multiple myeloma who have received at least three prior therapies	SAT	Overall Response Rate (ORR)	yes (supportive)	CMA
Breyanzi	relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.	SAT	Overall Response Rate (ORR)	yes (supportive)	full MA
carvykti	relapsed and refractory multiple myeloma, who have received at least three prior therapies.	SAT	Overall Response Rate (ORR)	yes (supportive)	CMA
Upstaza	aromatic L-amino acid decarboxylase (AADC) deficiency	SAT	Achievement of key motor milestones at the 2-year time point	yes (supportive)	MAUEC
Roctavian	severe haemophilia A	SAT	Change of hFVIII activity by chromogenic assay during Weeks 49-52 post-BMN 270 infusion from baseline.		CMA
Ebvallo	relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy	SAT	Overall Response Rate (ORR)	yes (supportive)	MAUEC
Hemgenix	severe and moderately severe haemophilia B	SAT	Annualised bleeding rate comparison between AMT-061 and prophylaxis for non-inferiority between the lead-in phase and the 52 weeks following stable FIX expression (		CMA
Casgevy	β-thalassemia (TDT) and sickle cell disease	SAT	TI12, defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion.		CMA
Beqvez	severe and moderately severe haemophilia B	SAT	Non-inferiority on ABR for total bleeds versus usual care FIX prophylaxis replacement regimen, comparing pre- and post-IP infusion.		CMA
Vyjuvek	dystrophic epidermolysis bullosa (DEB)	intrasubject RCT	complete wound healing at 6 months, defined as complete wound closure at weeks 22 and 24 or weeks 24 and 26		full MA
Aucatzyl	relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukaemia	SAT	Overall Response Rate (ORR)	yes (supportive)	CMA

SAT example: Zolgensma

- Gene therapy for the treatment of spinal muscular atrophy, replacement deficient gene.
- SAT with external natural history comparator
- Survival benefit clear → positive B/R



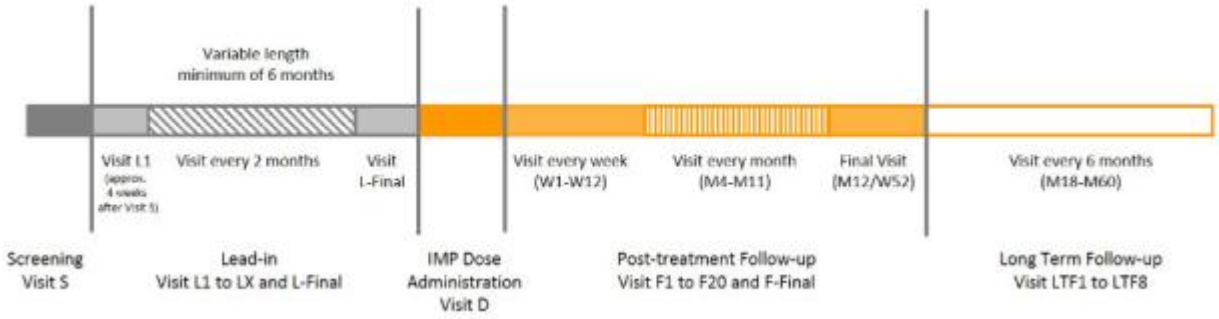


Source: Study CL-303 Figure 14.2.4.1.1

SAT example: Hemgenix

- AAV-based gene therapy
- Haemophilia B

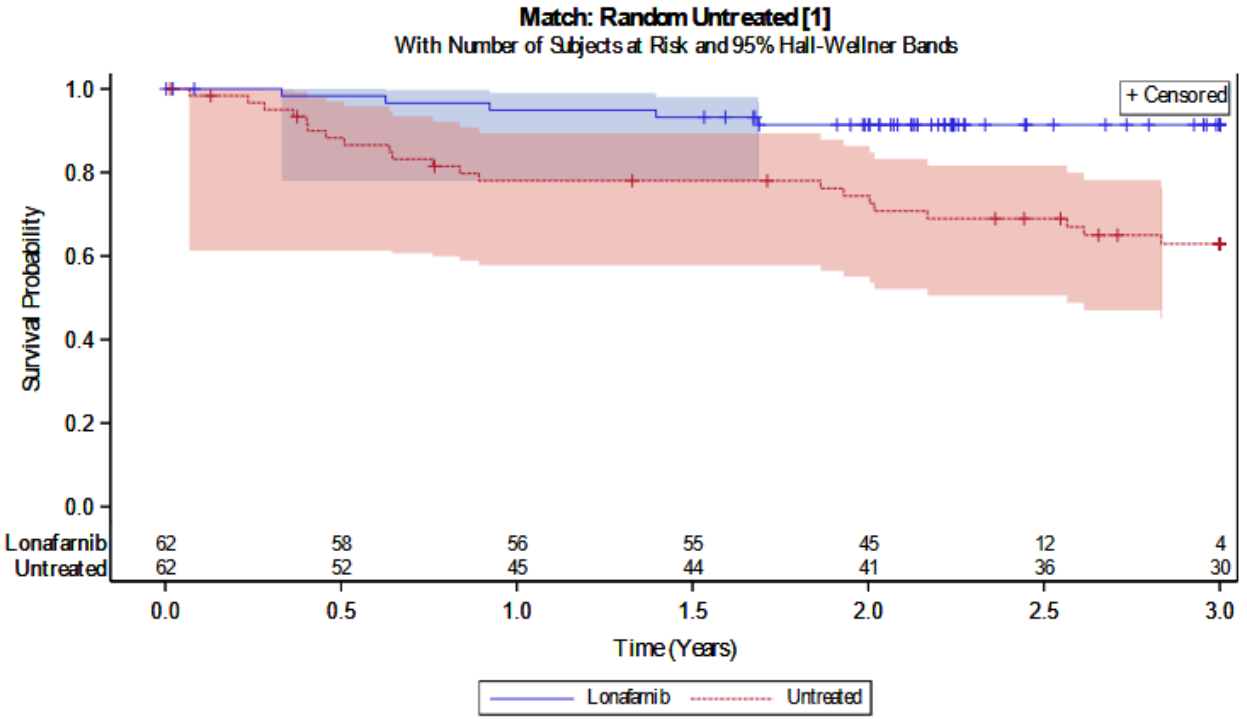
- ABR compared intra-subject
- Lead in phase and post-treatment FU



	Spontaneous Bleeding Episodes			FIX-treated Spontaneous Bleeding Episodes		
	≥6-month Lead-in Period (N = 54)	Month 7-18 (N = 54)	Month 7-24 (N = 54)	≥6-month Lead-in Period (N = 54)	Month 7-18 (N = 54)	Month 7-24 (N = 54)
Number of Subjects With a Bleeding Episode, n (%)	24 (44.4)	9 (16.7)	11 (20.4)	22 (40.7)	6 (11.1)	8 (14.8)
Cumulative Number of Bleeding Episodes, n	50	14	18	44	11	15
Cumulative Number of Person-years Observed, n	33.12	49.78	74.56	33.12	49.78	74.56
Unadjusted ABR[1]	1.51	0.28	0.24	1.33	0.22	0.20
Adjusted ABR (95% CI)[2]	1.52 (1.01, 2.30)	0.44 (0.17, 1.12)	0.38 (0.16, 0.89),	1.34 (0.87, 2.06)	0.45 (0.15, 1.39)	0.42 (0.15, 1.19)
Rate Ratio (Post-treatment/ Lead-in)[2]		0.29	0.25		0.34	0.31
Two-sided 95% Wald CI[2]		0.12, 0.71	0.11, 0.57		0.11, 1.00	0.11, 0.87
p-value[3]		0.0034	0.0005		0.0254	0.0127

SAT example: Lonafarnib

- Progeria
- MoA was not well defined
- Many uncertainties around the NHC
- Relevance of treatment effect? → 6 months survival benefit after 3 years of treatment.
- Very rare and high UMN → product approved UEC



But is does not always work!

- Unsuccesfull MAA with SAT as pivotal trial
  - Common disease
  - SAT
  - PRO as primary endpoint
  - Insufficient support from “hard” clinical secondary endpoints

Future outlook

- Many scientific advises where study design (SAT) is subject of advice
- Challenges and foreseen issues do not always lead to adaptation of study design
- Sometimes FDA has already endorsed the study

- Development of reflection papers and guidance on the use of external (RW) control data.
- SAT have been and will be an important source of evidence for ATMPs.

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