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Adaptive Enrichment Population Design Rare Epileptic Syndromes

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Introduction

Main features:

- Found in oncology study settings with potential for other therapeutic areas
- Able to address scientific & commercial questions
- High advanced cost and effort
- Overall potential to be time and cost-efficient

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Population Enrichment in CNS

- Versatility of design:
  - May be of particular interest in phase 2 development of novel anti-epileptics (AEDs)
  - Allows leap frogging
  - Could be suitable for groups of distinct syndromes found within Epileptic Encephalopathies(EE)

EE

- EE relate to a heterogeneous group of diseases
  - Lennox Gastaut Syndrome (LG), Dravet Syndrome (DS) and cyclin- dependent kinase-like 5 (CDKL5) Syndrome.
- Pathogenic factors may include genetic mutations related to synaptic, metabolic and inflammatory associated mechanisms
  - Epileptic activity contributes to different developmental outcomes
  - Selected AEDs have shown to be effective in reducing seizure types in some EE syndromes

Cross eta, 2016; Lague et. al., 2016; Chiron et al., 2016: Thiele et al., 2016

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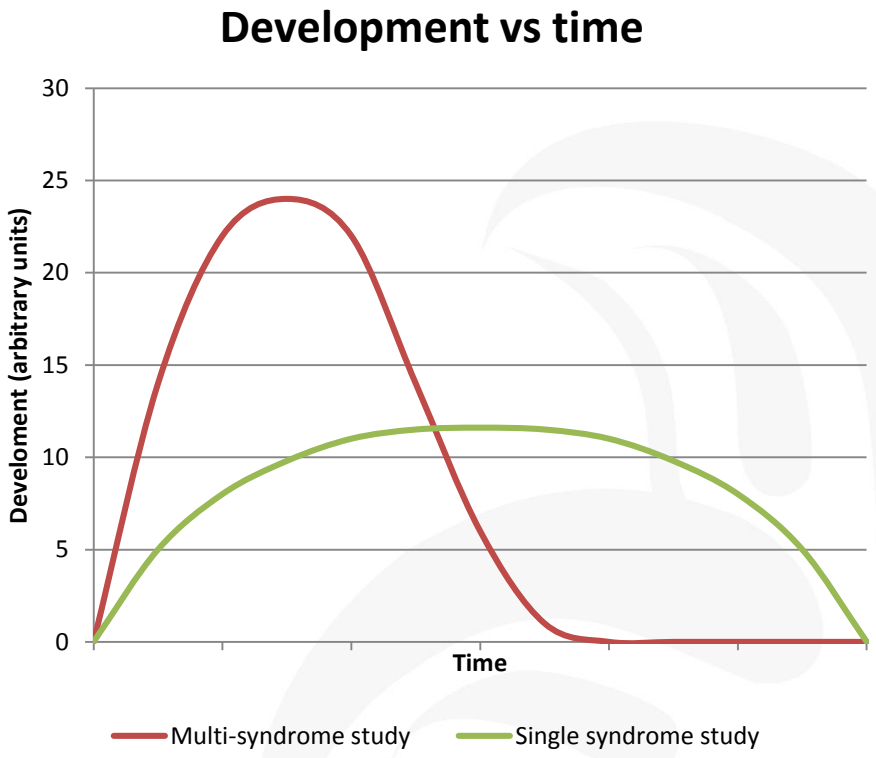
Unmet Medical Need



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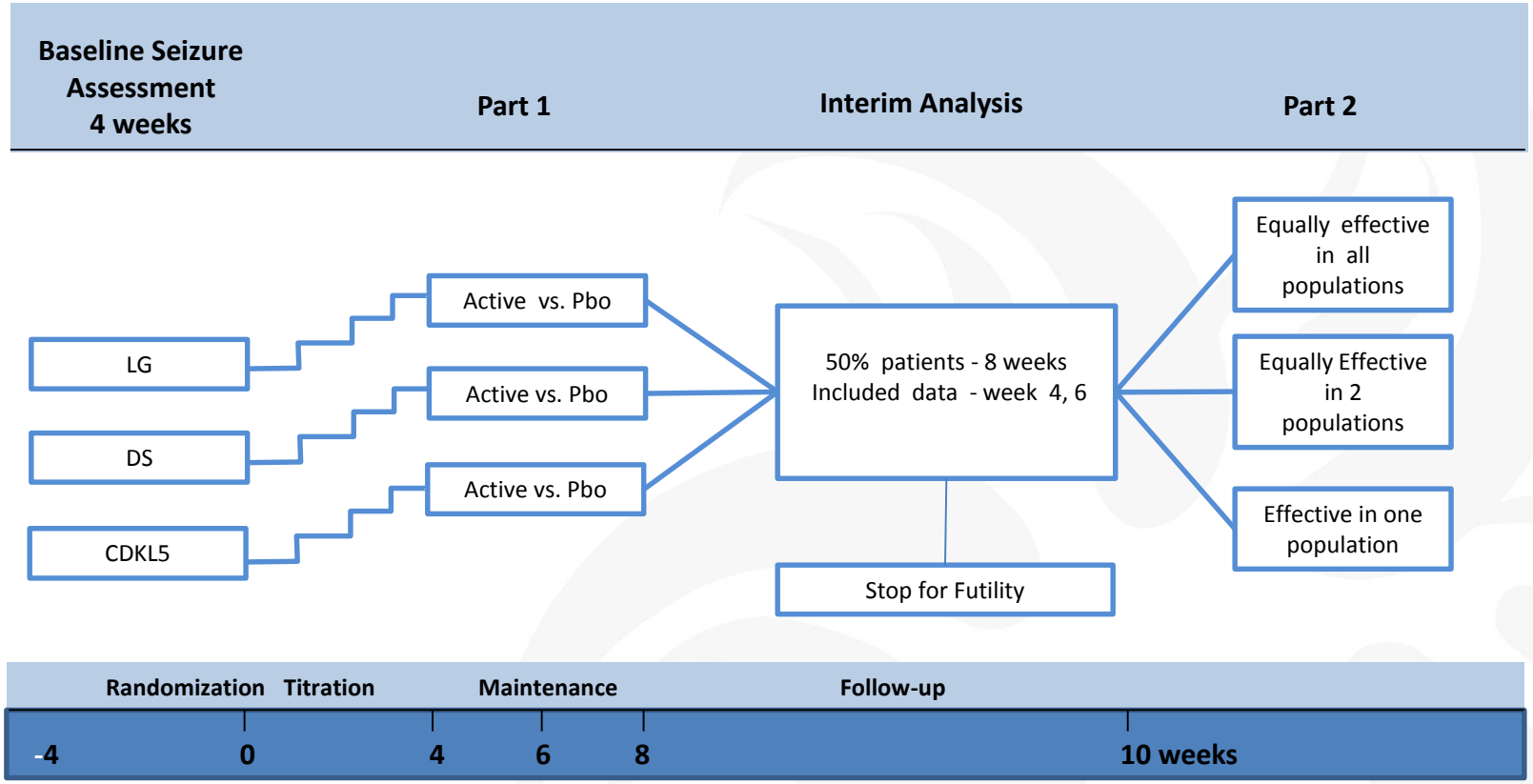
Objectives

- Demonstrate clinical efficacy in at least one population of interest (proof–of-efficacy)
- Learn whether the drug affects other domains such as cognition and/or behaviour
- Continued safety/tolerability assessment

Proposed Study Design



IA: restrict population and redirect sample size or stop for futility

LG- Lennox Gastaut Syndrome: DS- Dravet Syndrome: CDKL5- cyclin- dependent kinase –like 5: Pbo-placebo

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Simulation Considerations

- Data:
  - 60% target seizure response rate vs 10% placebo
  - 2:1 randomisation
    - Alpha 0.05: 2-sided
  - Aimed to achieve at least 90% power
    - Treatment has expected effect in all subgroups
  - Futility criterion
    - Risk difference 30% in the 'best' population
  - Exploratory endpoints excluded from the simulation but included in the study

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Simulation: Population Treatment

Scenario	Treatment Response Rate	Adaptive Test Power	Exact Population Selection	Mean Sample Size	Futility at IA
1	$P_1=P_2=P_3=60\%$	97%	73%	89	1%
2	$P_1=P_2=60\%$, $P_3=10\%$	83%	66%	87	7%
3	$P_1=60\%$ $P_2=P_3=10\%$	36%	45%	78	27%
4	$P_1=P_2=P_3=10\%$	N/A	N/A	47	95%

P1-population : LG, P2- population DS: P3- population CDKL5
100,000 simulations per scenario

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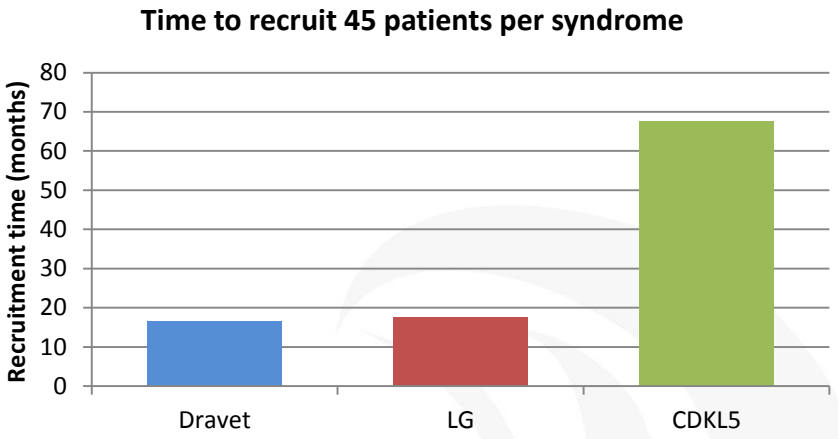
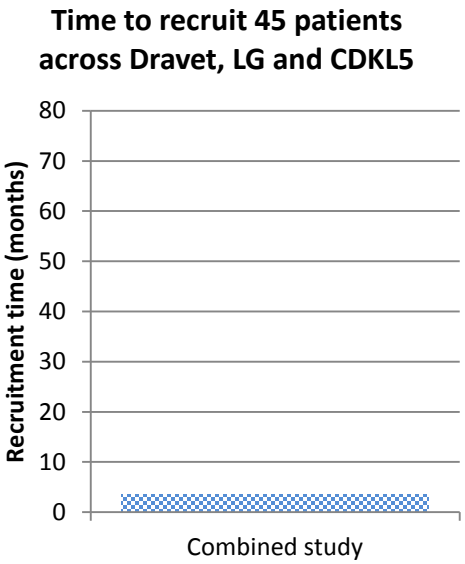
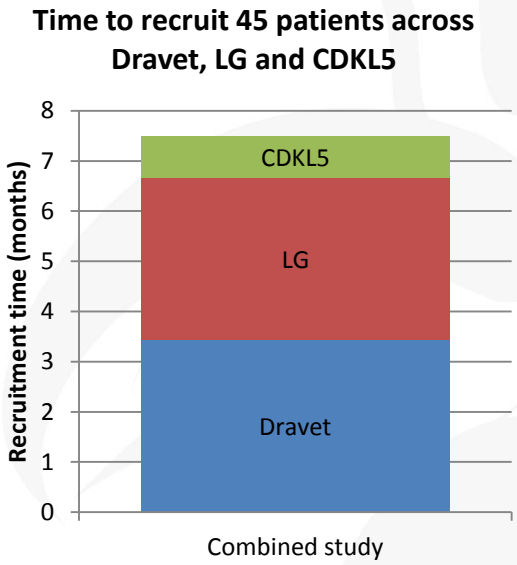
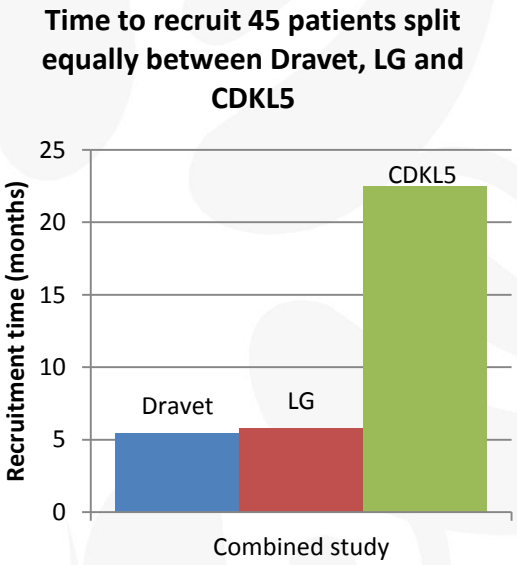
Logistics









Open Label Study: Data adapted from Devinsky et al., Lancet Neurology: 2016:15: 270-7B

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Decision Flow

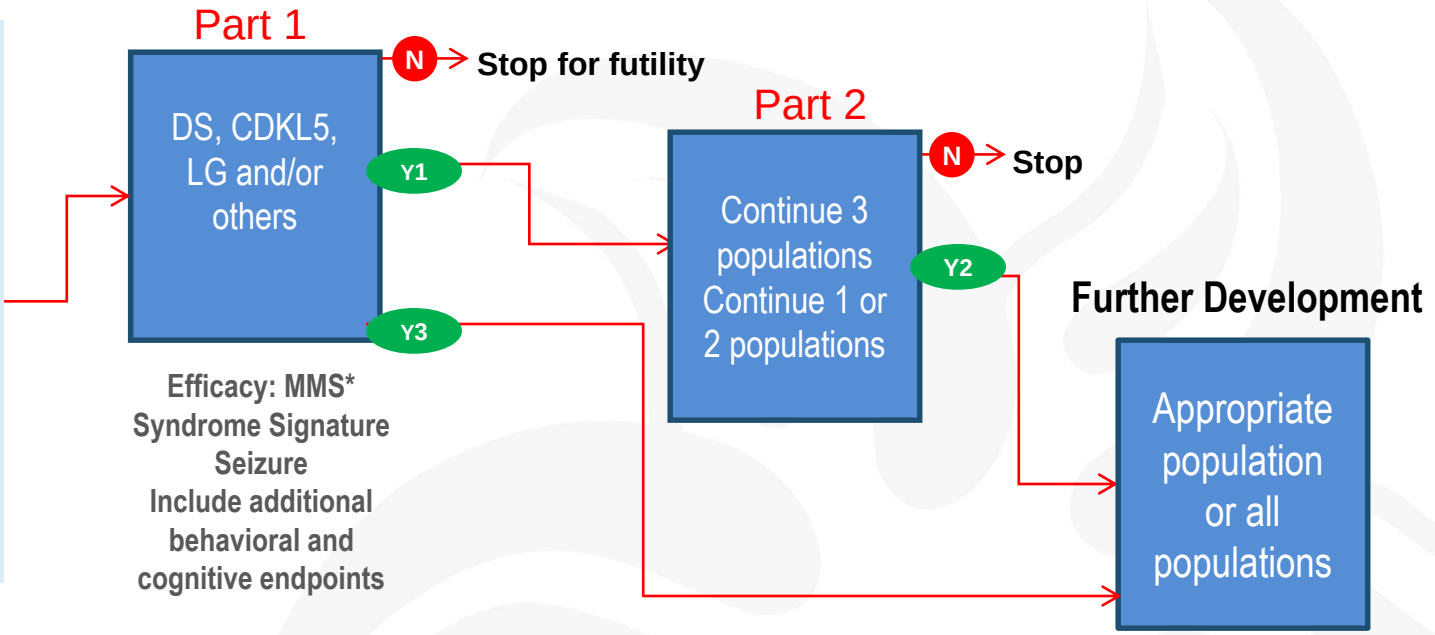
Proof-of-Efficacy

Evidence:

(1) Antiepileptic effects in at least one EE syndrome model and/or possibly other relevant animal models

(2) Early data includes PK/PD modelling and dose selection information

(2) Safety & Tolerability Data supportive of development in pedriatric populations



Major Motor Seizures (MMS)*

1) GTC, tonic, atonic, and focal seizures with motor component

Y1
Y2
- No safety signal to preclude further development
- Efficacy: Percentage reduction in seizure frequency at least one population

Y3
- No safety signal to preclude further development
- Robust Efficacy observed in all 3 populations:

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Conclusion

- Adaptive enrichment design
  - Higher advanced investment may be required
  - Early identification of population for compound suitability
  - May go a long way in differentiating a drug at the early stage of development
    - Assessment of time to next seizure endpoint can be added
  - The clinical programme appears accelerated and cost-effective.

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