Preliminary baseline results from the CANDID study: An observational study in patients with CDKL5 Deficiency Disorder

Liogier d'Ardhuy X.[1], Aimetti A.[2], Di Nardo A.[3], Cleary E.[4], Cimms T.[5], St Wecker P.[4], Rizzo M[3].

[1] Loulou Foundation; [2] Marinus Pharmaceuticals; [3] Biogen; [4] UCB Biosciences; [5] Ultragenyx Pharmaceutical

xliogier@louloufoundation.org

Background

First identified in 2004 as a distinct clinical monogenic disorder, CDKL5 (cyclin-dependent kinase-like 5) Deficiency Disorder (CDD) is a rare, pediatric, neurodevelopmental disorder caused by X-linked mutations in the CDKL5 gene and a deficiency of functional CDKL5 protein. Recent preclinical experiments using enzyme replacement or gene therapies have shown promising results and could be the future of drug development in CDD. A pre-competitive collaboration has been created aiming at harmonizing the clinical endpoint selection for potential efficacy trials in CDD.

Objectives

To design robust efficacy trials in CDD, we are conducting a global, longitudinal observational, non-drug study, in patients with CDD: the **CANDID** study (ClinicalTrials.gov identifier: NCT05373719).

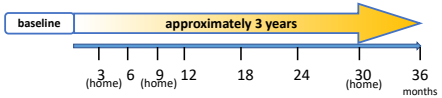
The aim of this study is to identify the best motor, cognitive and behavioral outcome measures in assessing their suitability. Here, we present baseline data from the enrolled participants.

Methods

- This study is a multi-centre (22), multi-country (USA, Canada, France, Spain, Italy, Germany, UAE), longitudinal study.
- Study population:
  - 100 individuals, diagnosis of CDD with pathogenic or likely pathogenic CDKL5 variants.
  - Of both genders, from birth to 55 years.
- Assessment:

DOMAINS	TESTS AND SCALES	REPORT TYPE
CLINICAL MEASURES	• Medical history/clinical interview * • Physical and neurological examination * • Seizure type, frequency and duration, as collected via parent / caregiver seizure diary • Sleep duration and quality collected using the Sleep Disturbance Scale for Children (SDSC)	• Clinician • Clinician • Caregiver • Caregiver
COGNITION AND GLOBAL DEVELOPMENT	• Bayley Scale of Infant and Toddler Development, Fourth Edition (BSID-4) • Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)	• Performance tool • Performance tool
BEHAVIOR	• Vineland Adaptive Behavior Scales, Third Edition (Vineland 3, interview form) • Aberrant Behavior Checklist (ABC-C)	• Caregiver • Caregiver
FUNCTIONING LEVEL	• Gross Motor Function Measure (GMFM) • Cortical Visual Impairment - Range (CVI-Range) • Caregiver Global Impression of Severity and Change (Care GI-S/C)	• Performance tool • Clinician • Caregiver
QUALITY OF LIFE & FAMILY IMPACT	• Quality of Life Inventory – Disability (QI-Disability) • The Short Form 12 Health Survey Version 2 (SF12-HS)	• Caregiver report • Caregiver report

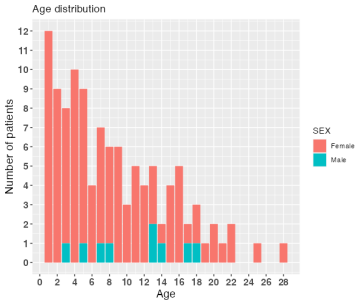
Study Design



Demographics

	Age at enrollment (Y:M)				Total
	0:0 to 2:0 (N=21)	2:1 to 6:0 (N=27)	6:1 to 13:0 (N=35)	13:1 to 45:0 (N=29)	N=112
Age at enrollment – years					
Mean	1.4	4.0	8.8	17.2	8.4
Range	<1-2	3-5	6-12	13-28	7.0 <0.5-28
Sex – n (%)					
Male	0 (0)	2 (7)	2 (6)	5 (17)	8%
Female	21 (100)	25 (93)	33 (94)	24 (83)	92%
First seizure onset - months					
N					110
Mean	-	-	-	-	3.4
Median					1.5
Min to max					0-66
Number of anti-seizure medication					
N	17	21	29	25	92
Mean (SD)	1.7 (0.86)	2.1 (0.97)	2.1 (0.98)	2.2 (1.00)	2.1 (0.94)
Min to max	1-3	1-4	1-5	1-4	1-5

Excluding rescue meds or PRN



Seizures

Seizure types (% of patients)	0-2y N=14	3-5y N=13	6-12y N=24	≥13y N=21	Total N=72
Major motor *	21.9	41.1	37.4	27.0	31.9
Spasms	42.4	24.9	23.5	21.1	27.0
Focal	1.3	-	17.1	18.1	11.3
Myoclonic	15.1	18.1	8.3	4.6	10.3
Atonic	8.6	6.8	11.5	7.4	9.0
Absence	-	8.1	2.0	15.2	6.3
Other	5.5	1.0	-	6.5	3.1
Tonic/atonic (unknown)	5.2	-	0.2	-	3.1
Patients with >16 seizures a month	**77**	**83**	**95**	**75**	**83**

** Includes clonic bilateral, tonic bilateral, generalized tonic-clonic*

➔ 8% are male participants; the oldest patient is 28y; the median first seizure onset is 1.5 months, and the mean number of AED was 2.1 at enrollment.

➔ 6 participants were seizure free for several years. The most frequent seizures were infantile spasms before the age of 3 (42%) and motor seizures in other age groups. 83% had more than 16 seizures per 28 days.

Co-occurring Conditions

	Type	Frequency (%)
CNS	Muscle tone abnormality	40
	Coordination disturbances/dyskinesia	16
	Speech abnormalities	10
Gastro-intestinal disorders	Atonic and hypomotility	61
	Gastrointestinal signs and symptoms	15
	Nausea and vomiting	5
Psychiatrics	Sleep disorder	42
	Stereotypies	21
	Pervasive developmental disorder	7

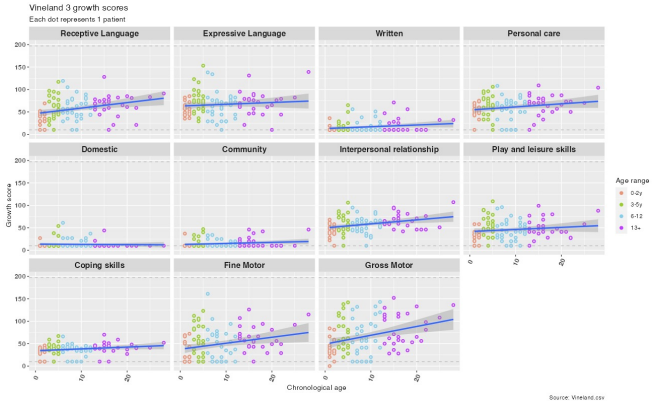
➔CNS, gastrointestinal and psychiatric disorders were the top 3 most frequently high-level impairments recorded.

➔ Aside seizures and intellectual disability which are core symptoms of the disease, muscle tone abnormalities, Atonic / hypomotility and sleep disorders were the most frequently reported.

Summary of findings

DOMAIN	TEST NAME	SUMMARY OF FINDINGS
Sleep	SDSC	The "sleep initiation" domain was the most impacted across all age groups, followed by "excessive somnolence" and "sleep/awake transition". Suitable variability level in the scores.
Cognition & global development	Bayley 4	No floor effect on domain growth scores. Suitable variability level in the scores. Scores stable across age groups. Functioning level of two patients compatible with the WPSSI administration (site feedback).
Behavior	- Vineland 3 - ABC-C	- See details. - Stereotypy, lethargy and irritability were the most impacted domains in all age groups. Suitable variability level in the scores.
Functioning level	- GMFM - CVI-Range - Care-GI-Severity	- **Floor effects** were observed in all age groups for Crawling, Standing and Walking dimensions, more specifically for the youngest age group where 62-95% of the participants were at floor; operational and scoring challenges identified (e.g. a zero score in one dimension prevent evaluations of next levels). - No differences across age groups. Mean scores around 40% (i.e. clear CVI). **High inter-subject variability**. Exploratory tool. - No major differences across age groups. About 70% of the parents considered their child as significantly ill or beyond (scores ≥5).
Quality of life & family impact	- QI-Disability - SF12-HS	- See details. - No age group differences. Mental component significantly impacted (physical component preserved). High inter-subject variability.

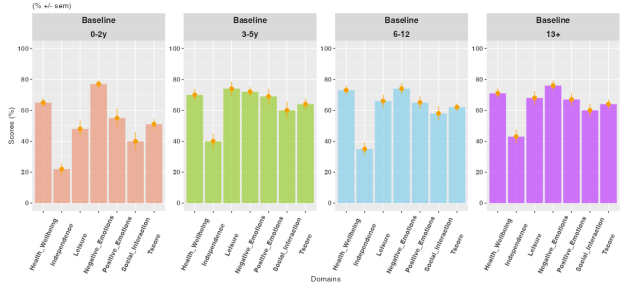
Adaptive Behavior (Vineland 3 - GSV)



➔ Only 3 domains «at floor» (Written/Domestic/Community).

➔ Improvement of scores over age, especially for the motor function.

Quality of Life (QI-Disability)



➔ No relevant differences in the total score between the different age groups (51-64%) suggesting a similar impact on global quality of life across the age groups. The lowest scores were recorded for the "independence" domain.

Conclusions

- CANDID study fully recruited and now collecting 3 years of prospective data.
- We identified the most suitable clinical sites for future clinical trials in CDD patients.
- 90% of our participants are below 18, and baseline characteristics are consistent with previous publications.
- Baseline data from the CANDID study demonstrated the feasibility and suitability of the Vineland 3 interview form, or the Bayley 4 for the assessment of adaptive function and neurodevelopment in future clinical trials with CDD patients. The GMFM revealed some operational and scoring weaknesses as a potential CDD endpoint.

Disclosure: CANDID pre-competitive consortium, co-funded by Amicus, Biogen, Elaaj Bio, Marinus, PTC, UCB, Ultragenyx. OPEN to new members