

Pediatric plans optimization of C.E.R.A. (Continuous Erythropoietin Receptor Activator): clinical evidence obtained through a model-based integration of multisource data



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1 – Background and Objectives

- C.E.R.A. is a continuous erythropoietin receptor activator with a longer half-life compared with other Erythropoietin Stimulating Agents (ESA) such as epoetin beta, epoetin alfa, and darbepoetin alfa, allowing once-monthly dosing. C.E.R.A. treatment is dose-adjusted according to hemoglobin (Hb) levels.
- In adults, C.E.R.A. has been approved in Europe and US in 2007 and is indicated for the treatment of anemia associated with CKD in patients on dialysis and not on dialysis and is administered intravenously (IV) or subcutaneously (SC). C.E.R.A. is effective in correction (ESA naïve patients) and maintenance of Hb (switching from darbepoetin alfa or epoetin alfa/beta to C.E.R.A.)¹.
- In pediatric patients, C.E.R.A. is used to maintain Hb levels after correction by another ESA.
- Roche also submitted a Pediatric Investigation Plan (PIP) and a Pediatric Study Plan (PSP) for C.E.R.A. As part of the pediatric development plans, an open-label Phase II study (DOLPHIN, NH19707) of intravenous (IV) C.E.R.A. in patients aged 5–17 years was conducted. The DOLPHIN study was conducted to determine the optimum dose conversion factor between darbepoetin alfa or epoetin alfa/beta and C.E.R.A. in pediatric CKD patients. Patients on hemodialysis with stable chronic anemia were switched to IV C.E.R.A. for 20 weeks. The data collected in this trial was analyzed with adult IV and SC data.
- The established optimum dose conversion factor is 4x previous weekly darbepoetin alfa dose divided by 0.55 or 4 x previous weekly epoetin dose divided by 125.
- The objectives were to determine the pharmacokinetic (PK) and pharmacodynamic (PD) (PK/PD) characteristics of C.E.R.A. in a broad population and, using simulations, to optimize the design of a second pediatric study using SC administration of C.E.R.A. (NH19708) and thus support PSP and PIP.

3 – Results: PK and PK/PD models

Parameters estimates of the population PK model

Parameter	Estimate	SE	RSE (%)	Variability (%)	Shrinkage (%)
Fixed effects					
CL (L/day)	0.738	0.0231	3		
V (L)	3.46	0.143	4		
Ka-Ke (/day)	0.198	0.0616	31		
F	0.326	0.0200	6		
Random effects (variance)					
CL	0.202	0.0317	16	45	7
V	0.135	0.0242	18	37	16
Covariance CLxV	0.111	0.0274	25	correlation 0.68	
Inter occasion variability on CL	0.0160	0.00344	22	13	
Covariate effects					
Body weight on CL	0.761	0.0665	9		
Body weight on V	0.612	0.0686	11		
Age on V	0.232	0.0383	17		
Residual variability (variance)					
Proportional	0.146	0.00736	5	38	
Additive	0.911	0.117	13		

-SE: standard error
-RSE: relative standard error
-CL: clearance
-V: volume of distribution
-Ka: absorption rate constant
-Ke: elimination rate constant
-F: bioavailability

Body weight and age effects on PK previously characterized on adult Phase III data were confirmed and shown very consistent across both populations².

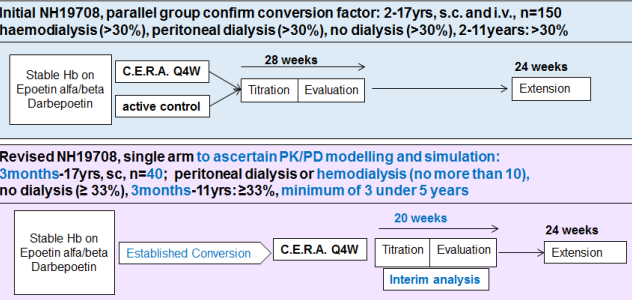
Parameters estimates of the population PK/PD model

Parameter	Estimate	SE	RSE (%)	Variability (%)	Shrinkage (%)
Fixed and random effects					
S _{max}	0.425 fixed			142	15
SC ₅₀ (ng/mL)	0.898 fixed			222	16
LS (day)	61.3 fixed			53	16
Hb ₀ (g/dL)	9.3 fixed			24	25
Covariate effects					
ESA dose on SC ₅₀	0.389	0.0234	6.0		
Body weight on Hb ₀	0.144	0.0102	7.1		
Residual variability (standard deviation)					
Additive (g/dL)	0.583	0.00116	0.2		

The historical PK/PD model was re-evaluated with re-estimation of inter-individual variability terms and covariates effects were revisited².

4 – Conclusions

- The PK/PD characteristics of C.E.R.A. are similar between adult and pediatric populations.
- The SC study design was simulated assuming a reduced number of subjects (N=25) compared to the one foreseen in initial pediatric plans (N=150).



- Revised pediatric plans were approved by FDA and EMA

5- References

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2 – Methods

- A modeling and simulation (M&S) framework that adequately describes C.E.R.A. concentration and Hb levels time courses, and that permits simulations according to different drug administration scenarios, has been previously developed using data from three Phase III randomized trials of C.E.R.A. in ESA-naïve and previously ESA-treated adult patients².
- This M&S framework consisted of PK and PK/PD models, it has been updated by pooling data from Phase II and III adult studies (N=524) with data from the DOLPHIN study (N=63) using NONMEM version 7.3.0. and Phoenix NLME 1.3.

Study	Phase	Route	Treatment Setting	Population	Number of patients Used in analysis/Total
BA16260 ³	II	SC	Correction	Adult on dialysis	59/61
BA16528 ⁴	II	SC	Correction	Adult not on dialysis	65/65
AMICUS ⁵	III	IV	Correction	Adult on dialysis	135/165
MAXIMA ⁶	III	IV	Maintenance	Adult on dialysis	122/223
PROTOS ⁷	III	SC	Maintenance	Adult on dialysis	143/190
DOLPHIN⁸	II	IV	Maintenance	Pediatric on dialysis	N=63/64

- The historical PK model was a one-compartment model with first-order absorption and elimination processes. After adjustment for previously identified covariate effects of body weight and age, potential remaining trends between adult and pediatric patients were explored graphically.

$$Hb'(t) = S(t) - S(t - LS) + S_{ESA}$$
$$S(t) = \frac{Hb_0}{LS} \cdot \left(1 + \frac{S_{max} \cdot C(t)}{SC_{50} + C(t)} \right)$$
$$S_{ESA} = \frac{Hb_0 - Hb_{sw}}{LS} \text{ if } 0 \leq t \leq LS \text{ otherwise } S_{ESA} = 0$$

-Hb' ((g/dL)/d): change in Hb level over time
-S(t) ((g/dL)/d) and its LS-delayed value S(t - LS): production and elimination of Hb, respectively.
-LS (d): apparent life span of red blood cells
-Hb₀ (g/dL): Hb level at baseline before ESA treatment
-Hb₀/LS: production rate of Hb at baseline, constant during one LS
-Hb_{sw}: Hb at switch from ESA to C.E.R.A.
-S_{max}: maximum relative increase in Hb production rate
-SC₅₀ concentration of C.E.R.A. to achieve 50% of the max. increase

- Simulations of clinical outcomes in pediatric patients receiving C.E.R.A. SC were performed using the updated M&S framework to support the design of study NH19708. To account for a potentially higher bioavailability (F) in pediatric patients^{9,10,11} three scenarios were simulated: same F in pediatric compared to adult patients, and an increased in F by 30% and by 50%.
- Model inferences were challenged versus Real World Data (RWD) from registries maintained by the International Pediatric Dialysis Network (IPDN, www.pedpd.org). RWD were obtained in 107 pediatric patients receiving C.E.R.A. SC and 22 pediatric patients receiving C.E.R.A. IV.

3 – Results: Model-based integrations and simulations

