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Development of HLB3-002 (recombinant human PH20 stand-alone) and its applicability as an anticancer diffusion agent.

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Background: HLB3-002 is a standalone of Halozyme's rHuPH20 (Original) and has the same amino acid sequence. HLB3-002 is being developed as a drug diffusion agent that decomposes subcutaneous hyaluronan, allowing substances such as anticancer drugs to be administered subcutaneously. This study was conducted to compare the in vivo efficacy and PK of original and HLB3-002 to confirm equivalence and thereby prove its applicability as a drug diffusion agent. **Methods:** In the in vivo efficacy test, Trypan blue was mixed with each original and HLB3-002 and administered subcutaneously to confirm diffusion and reconstruction equivalence in the nude mouse. The PK test was conducted using Rituximab, prepared in the same formulation as Rituximab SC by adding HLB3-002. A single dose was administered subcutaneously to the nape of the rat, and 12 points were collected for 28 days. The PK samples were measured by ELISA. When the C_{max} and AUC_{last} ratios of Rituximab between 2 groups were within 80.00 to 125.00%, they were evaluated as biologically equivalent. **Results:** As a result of efficacy test, the diffusion area of HLB3-002 was 104.7% compared to the original, which was confirmed to have an equivalent diffusion efficacy. In the skin reconstruction test, it was confirmed that both original and HLB3-002 rebuilt the skin layer to a similar to the negative control after 48 hours. As a result of the PK, Compared to Rituximab SC, the C_{max} of Rituximab+HLB3-002 was similar at 98.53% and AUC_{last} at 95.50%. **Conclusions:** Through an in vivo efficacy and PK test, we confirmed an equivalent drug diffusion effect, confirming that HLB3-002 applicability as an anticancer drug diffusion agent. Research Sponsor: None.

Diffusion, reconstruction and PK test.

A. Diffusion Test (n=5)	**0 min**	**2 min**	**5 min**	**10 min**	**20 min**	**P-value**
Original 5 Unit, Area (mm^2) (SD)	48.16 (7.72)	67.99 (8.48)	79.62 (8.52)	89.18 (9.91)	109.86 (13.70)	0.917
HLB3-002 5 Unit, Area (mm^2) (SD)	36.19 (4.49)	65.54 (9.29)	77.14 (5.83)	91.87 (8.40)	115.06 (8.03)	
B. Reconstruction Test (n=7)	**0.5 hr**	**1 hr**	**6 hr**	**24 hr**	**48 hr**	**P-value**
Original 5 Unit, Area (mm^2) (SD)	102.31 (18.54)	79.06 (4.33)	50.03 (4.91)	42.29 (3.26)	28.64 (3.71)	0.996
HLB3-002 5 Unit, Area (mm^2) (SD)	98.26 (11.96)	81.10 (4.08)	51.96 (6.77)	42.08 (2.01)	28.50 (2.56)	
C. PK Test (n=7)	**Cmax(μg/mL)**	**AUClast (day*μg/mL)**	**AUCinf (day*μg/mL)**	**Tmax(day)**	**t1/2(day)**	
G1, Aver (SD)	161.76 (24.81)	1861.23 (305.70)	1900.38 (349.49)	1 – 3	1.3 – 9.6	
G2, Aver (SD)	158.32 (11.59)	1762.51 (155.13)	1765.48 (155.54)	1 – 3	2.3 – 2.7	
G2/G1 (%)	98.53	95.5	93.97	-	-	

If the P-value is > 05, there is no statistical difference between the 2 groups. G1 is Rituximab SC, G2 is Rituximab + HLB3-002. AUC and Cmax values are expressed as mean ± standard deviation. Tmax and T1/2 values are expressed as a range. G2/G1 (%) value was calculated based on the geometric mean.