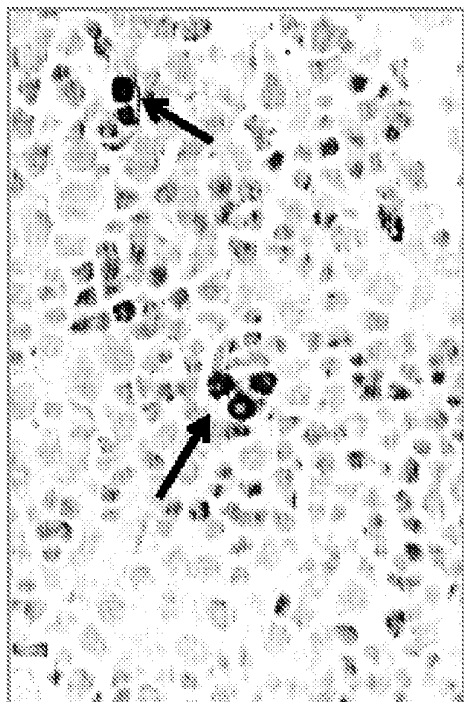
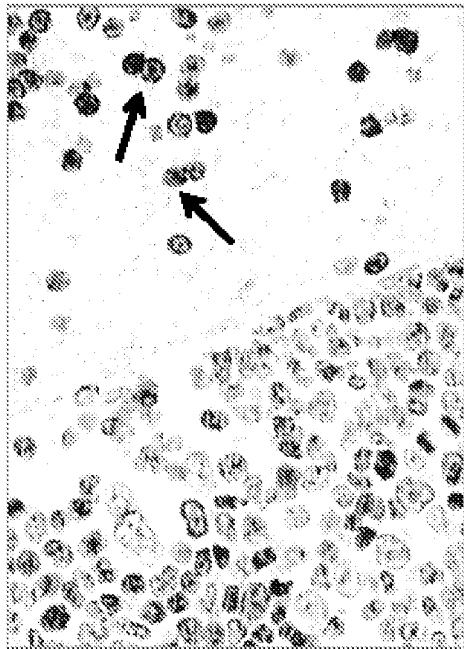


**Immuno-histochemical staining of PEG Moiety
within the CERA Structure in
the Bone Marrow Cells in Rats
(tissues obtained from the CERA treated rats)**



30 Min. Post Dose

At 30 min. post dose, heavy staining appears at the periphery of specific cells



24 Hr. Post Dose

Twenty-four hours later, stained cells had moved out of the marrow and into the blood stream.

Some of the staining appeared inside the cell membrane

Note that intact CERA reaches and binds the cells within the bone marrow

AutoDate

14

(Adopted from R00503821, Study No. D01017 & D02001 Report No. 1012588)

Summary of Non Clinical DMPK Results

- 1) Only intact CERA detected in the serum.**
- 2) Radioactivities detected in the bile and the liver.**
- 3) In both urine and the feces, radioactivities also detected.**
- 4) Both intact CERA and PEG moiety within the CERA structure detected in the urine.**
- 5) Intact CERA reaches and binds cells in the bone marrow.**

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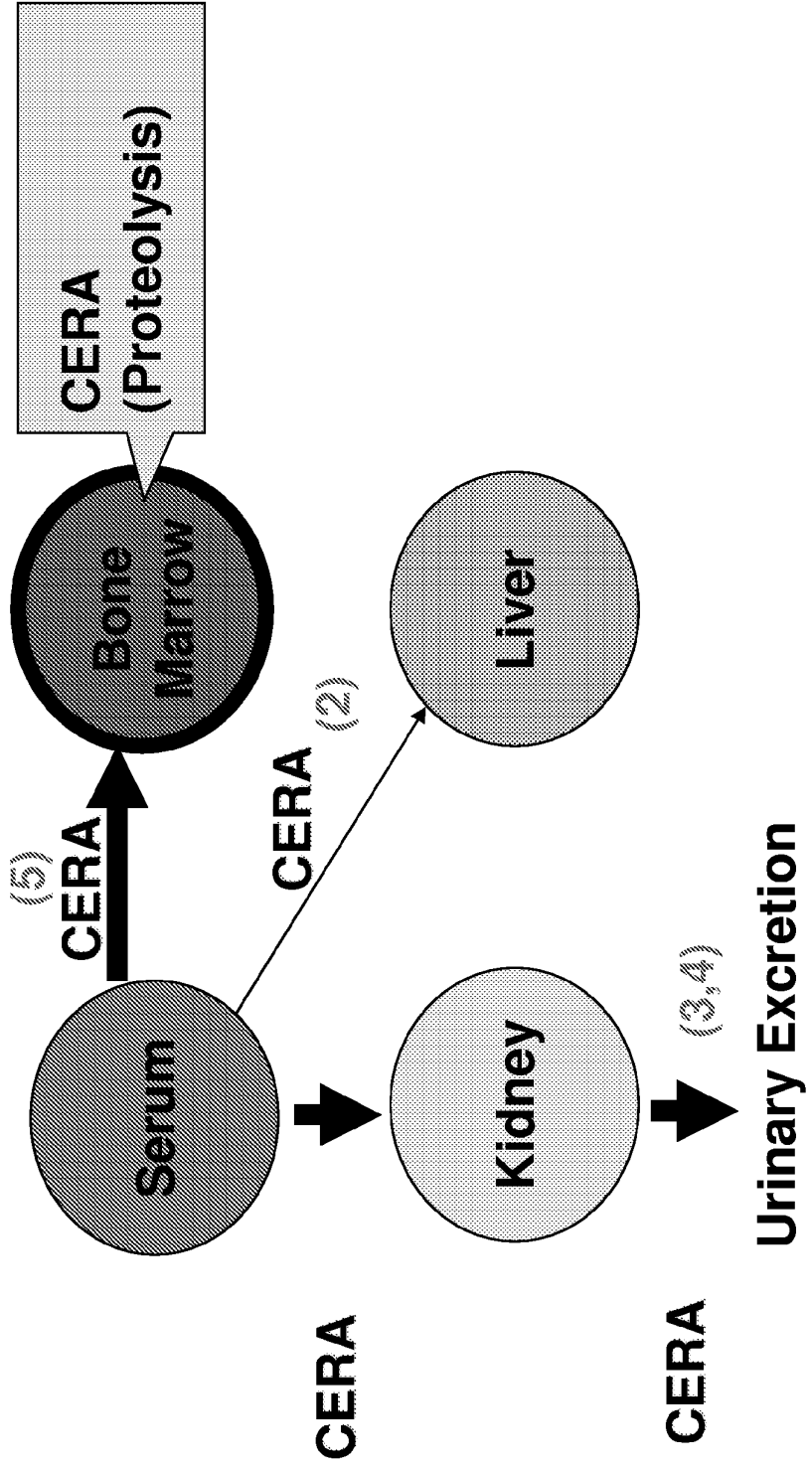
15

Speculative Diagrams (Rats)

AutoDate

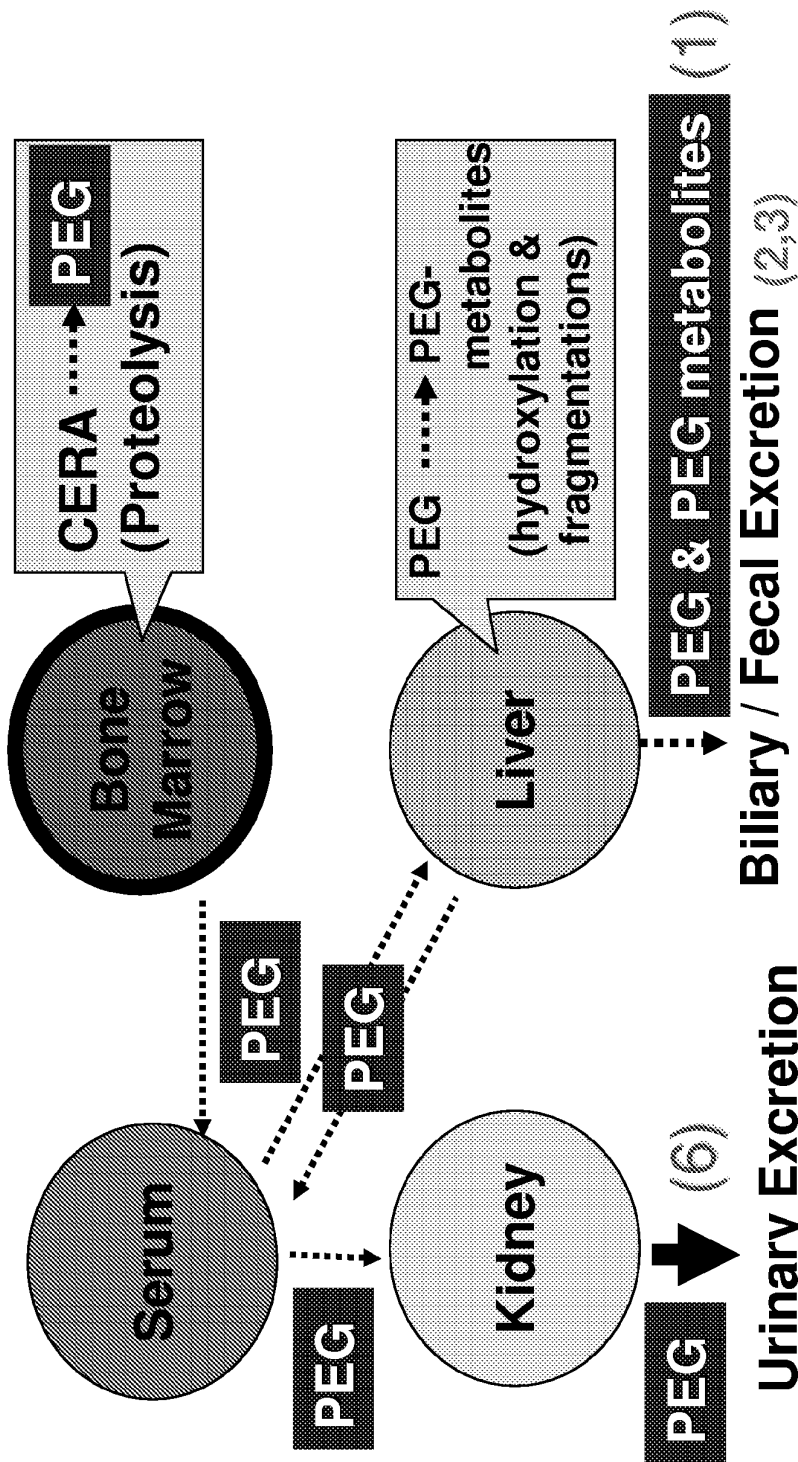
16

Suggested Elimination Pathways of CERA in Rats



The numbers in the parenthesis represent those appeared in the "Summary of Non Clinical DMPK Results" (p.15).

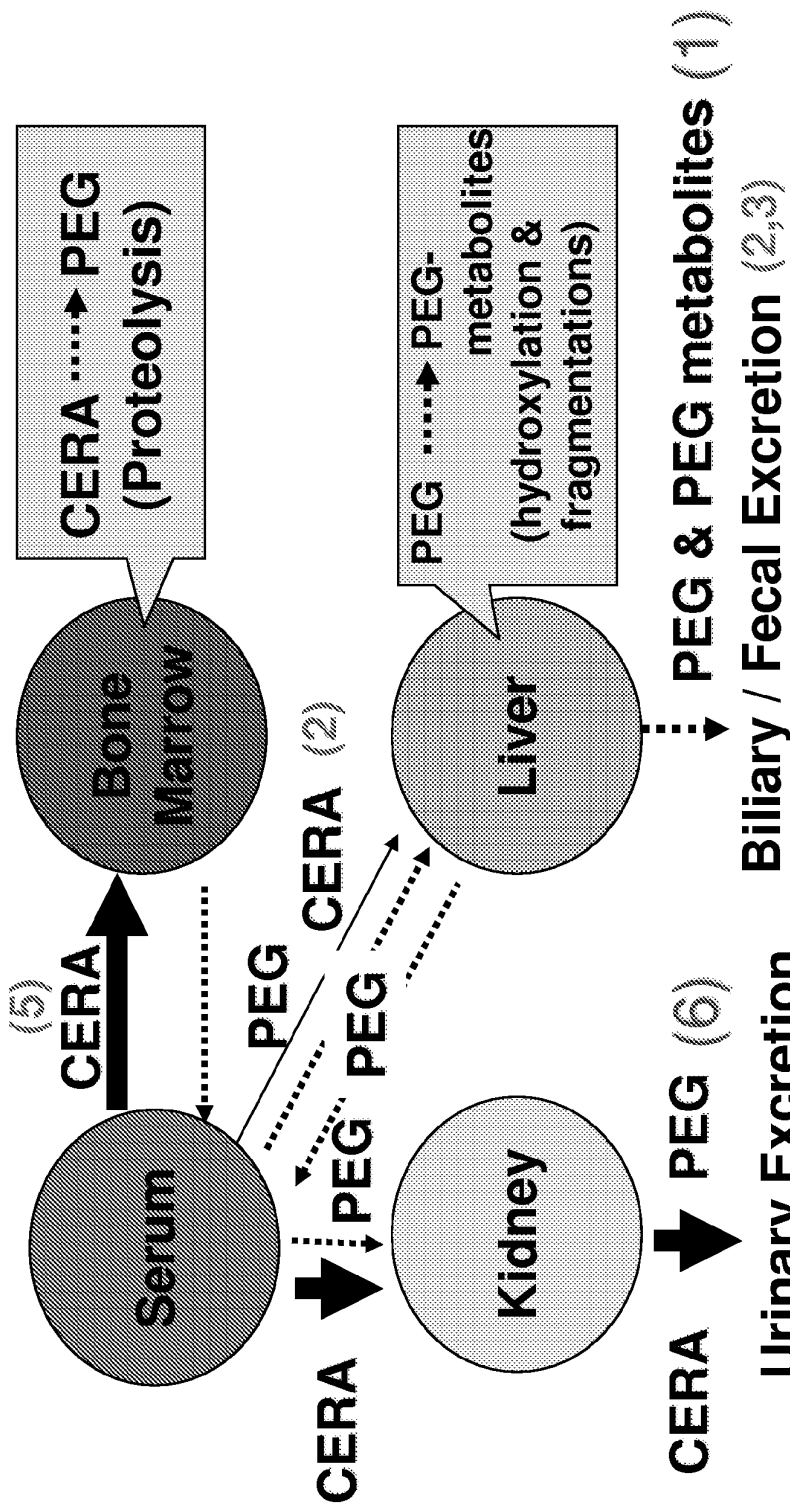
Suggested Elimination Pathways of PEG in Rats



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The numbers in red in the parenthesis represent the excretion rate.

Suggested Elimination Pathways of CERA & PEG in Rats (Summary)



← , Data available on CERA
 ←....., No data available on CERA

AutoDate

Part 2
Elimination Patterns of CERA
in Human

AutoDate

Urinary Excretion of CERA in Healthy Volunteers (HVs)

➤ *Routes of CERA Administrations*

S.C. administrations of CERA ($3.2 \mu\text{g/kg}$) to the HVs., and the urine was collected at an interval of every 12 hours for successive 3 days after the dosing.

➤ *Results*

No CERA was apparently detected in the HVs urine (No data available on the PEG moiety elimination patterns)

AutoDate

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(Adopted from RO0503821, Protocol No. BP16198 Report No. 1004598)

The immune system related to CERA elimination in Human

➤ **Clinical Data**

No Anti-CERA Antibodies detected in the Serum of CERA Treated HVs and Pts.

The concentrations of TNF- α and IL-6, which are cytokines reflecting activated macrophage, in the serum showed no relationship to AUC in CERA Treated HVs

➤ **Speculative Synthesis**

The immune system per se dose not seem to play crucial roles in the elimination of CERA

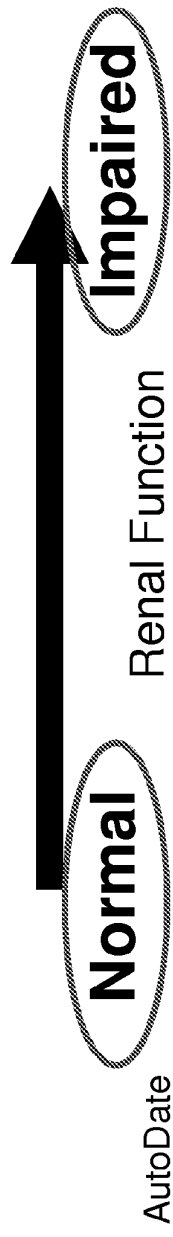
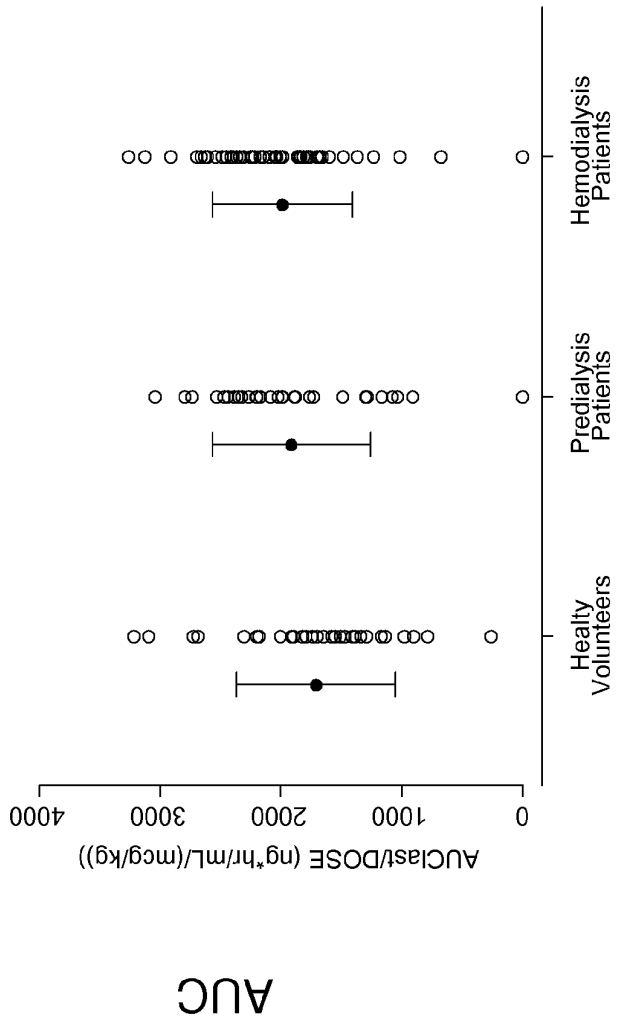
AutoDate

22

(Adopted from R00503821 all clinical studies and Protocol No.BP17570, Report No.1017562)

Relationships between Serum AUC and Renal Functions in Human (i.v. administrations of CERA to HVs & Pts)

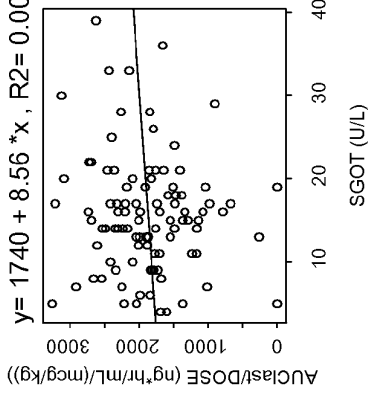
- No distinct relationship between serum AUC and renal functions were manifested
- These data strongly suggest that the kidney is not the main site by which the elimination of CERA is mediated



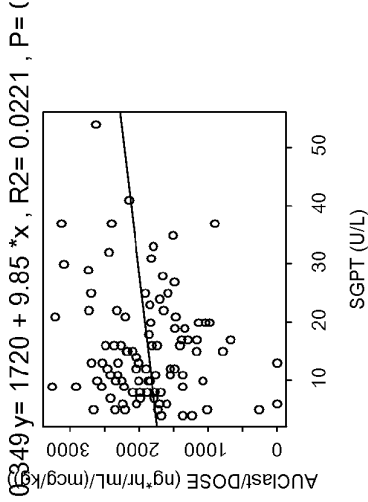
(Adopted from RO0503821 clinical studies, the integrated analysis of 5 (five) clinical studies in Japanese)

Relationships between Serum AUC vs. Hepatic Functions in Human (after i.v. administrations of CERA to HVs & Pts)

AUC vs. SGOT

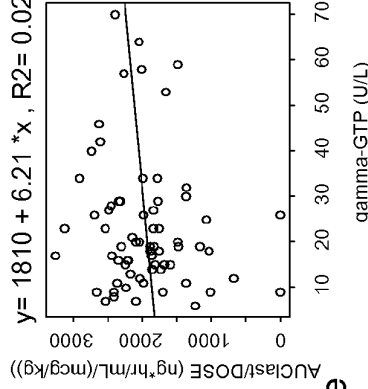


AUC vs. SGPT

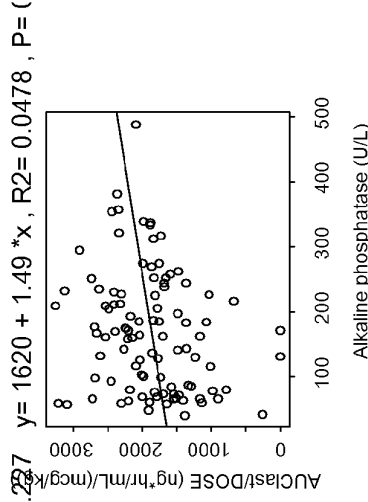


➤ No distinctive relationship between serum AUC and hepatic functions

AUC vs. γ-GTP



AUC vs. ALP



AutoDate

24

(Adopted from RO0503821 clinical studies, the integrated analysis of 5 (five) clinical studies in Japanese)

Summary of Clinical DMPK Results

- 1) *Intact CERA detected in the serum.*
- 2) *No intact CERA was apparently detected in the HVs urine.*
- 3) *No Anti-CERA Antibodies was detected in the Serum of CERA Treated HVs and Pts.*
- 4) *No distinct relationship shown between AUC and kidney/liver functions.*

AutoDate

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