

Suggested Elimination Pathways of CERA in CKD Patients

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Proposal to Roche

- *To investigate the metabolism and excretion patterns of ¹⁴C-CERA in nephrectomized rats.*
- *“The mass-balance studies using ¹⁴C-CERA” to be performed in PreD patients & HVs.*

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Special Remarks

- As far as the protein-based medicines are concerned, the Japanese Agency has never ever requested the metabolism patterns of the substance *per se* at the time of submissions.
- Essentially the same conditions can be applied to those in overseas.
- In the case of CERA, however, not a few investigators reported that the major elimination pathway of PEG is via an urinary excretion at least in the healthy volunteers (HVs).
- Due to the hypouresis manifested in CKD, it seems very likely that the PEG cannot be efficiently excreted into the urine.
- Therefore, the Japanese Agency will request the elimination patterns of the PEG moiety in CERA to Chugai.
- We believe it quite reasonable to prepare the answers as to the elimination patterns of CERA from the body.

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Elimination Pathways of EPO & PEG

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Elimination Pathways of EPO

- ***Major Elimination Pathways are within the “Bone Marrow & Spleen” that include,***
 - EPO Receptor-mediated Internalization, and
 - Proteolysis
- ***Those minors are within the “Kidney & Liver” that include,***
 - Glomerular Filtrations in the Kidney, and
 - Peptidase-mediated Catabolism in the Liver

Elimination Pathways of PEG

- ***Major Elimination Pathways are within the “Kidney & Immune System” that includes,***
 - Glomerular Filtrations in the kidney, and
 - Phagocytosis via the Immune System, particularly in the case of PEG m.w. is over 100 kDa
- ***That minor is within the “Liver” that include,***
 - **Metabolisms, i.e., Hydroxylation and Fragmentations, in the Liver, followed by**
 - **Biliary Excretion**

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Suggested Elimination Pathways of CERA

- 1. Rats**
- 2. Healthy volunteers**
- 3. Hemodialysis patients**

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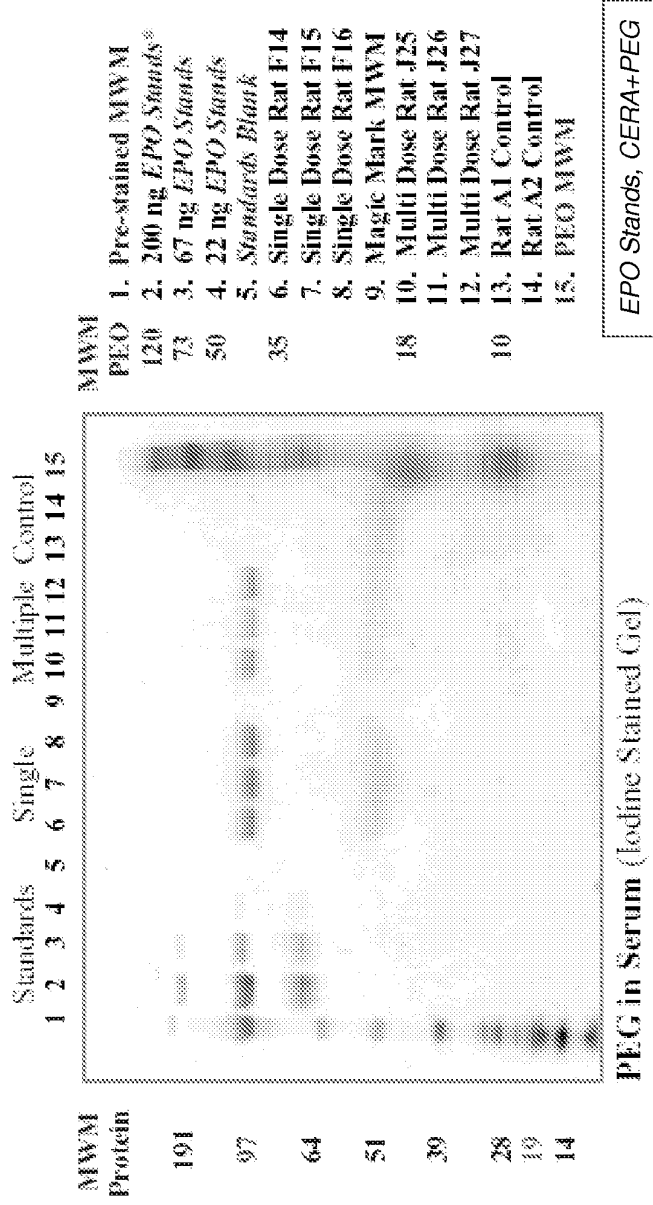
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Part 1
Elimination Patterns of CERA
in Rats

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Serum SDS-PAGE Patterns in Rats (serum obtained from the CERA treated rats)



Note that CERA remains intact in the serum

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

**Distribution & Excretion Patterns of
CERA after Single IV Injection to Rats**
(data obtained from studies using radioactive CERA)

- ***Tissues with high radioactivities
examined were,***
 - blood, bile, adrenal grand medulla,
lymph nodes, lung, testis, and adrenal gland

- ***% radioactivities detected after CERA
administrations were,***
 - urine (58 %), feces (8.6 %), and
carcass (33 %), respectively.
(% of CERA administered)

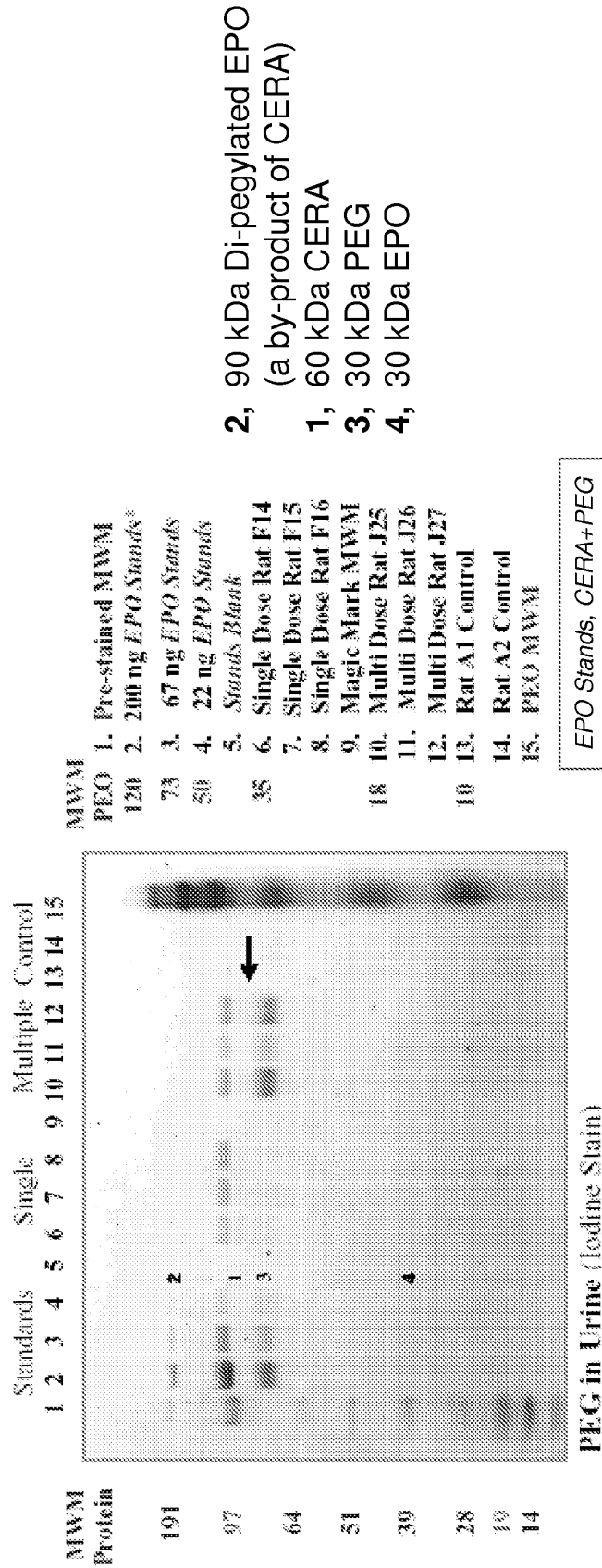
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(Adopted from RO0503821, Study No. 08223 Report No. 1014641)

Urine SDS-PAGE Patterns in Rats

(urine obtained from the CERA treated rats & iodine staining of PEG-moiety within the CERA structure)



Note that both intact CERA and 30kDa PEG are detected in the urine

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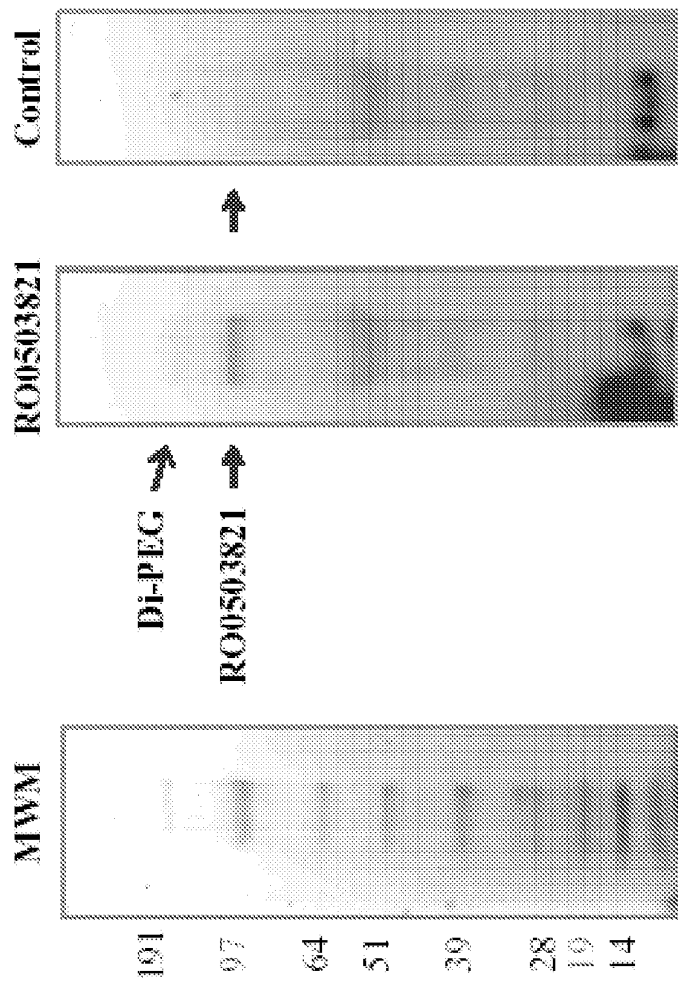
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(Adopted from R00503821, Study No. D01017 & D02001 Report No. 1012588)

Bone Marrow SDS-PAGE

Patterns in Rats

(aspirates obtained from the CERA treated rats)



Bone marrow cell supernatant from an RO0503821 treated rat and an untreated rat (control).

Note that intact CERA is detected in the bone marrow

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(Adopted from RO0503821, Study No. D01017 & D02001 Report No. 1012588)