ESETT PHARMACOKINETIC-PHARMACODYNAMIC (PK/PD) STUDY TRAINING

ESETT VIRTUAL INVESTIGATOR MEETING
OCTOBER 4, 2017

Lisa Coles, MS, PhD
Research Assistant Professor
Dept of Experimental and Clinical Pharmacology
University of Minnesota

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Rationale

- Substantial variability in drug concentrations occurs following administration of AED loading doses
- ESETT protocol uses a mg/kg basis for dosing capped at 75 kg
- Variability in early drug concentrations can be high even at the same mg/kg dose
- Unknown if drug concentrations correlate with efficacy in management of SE

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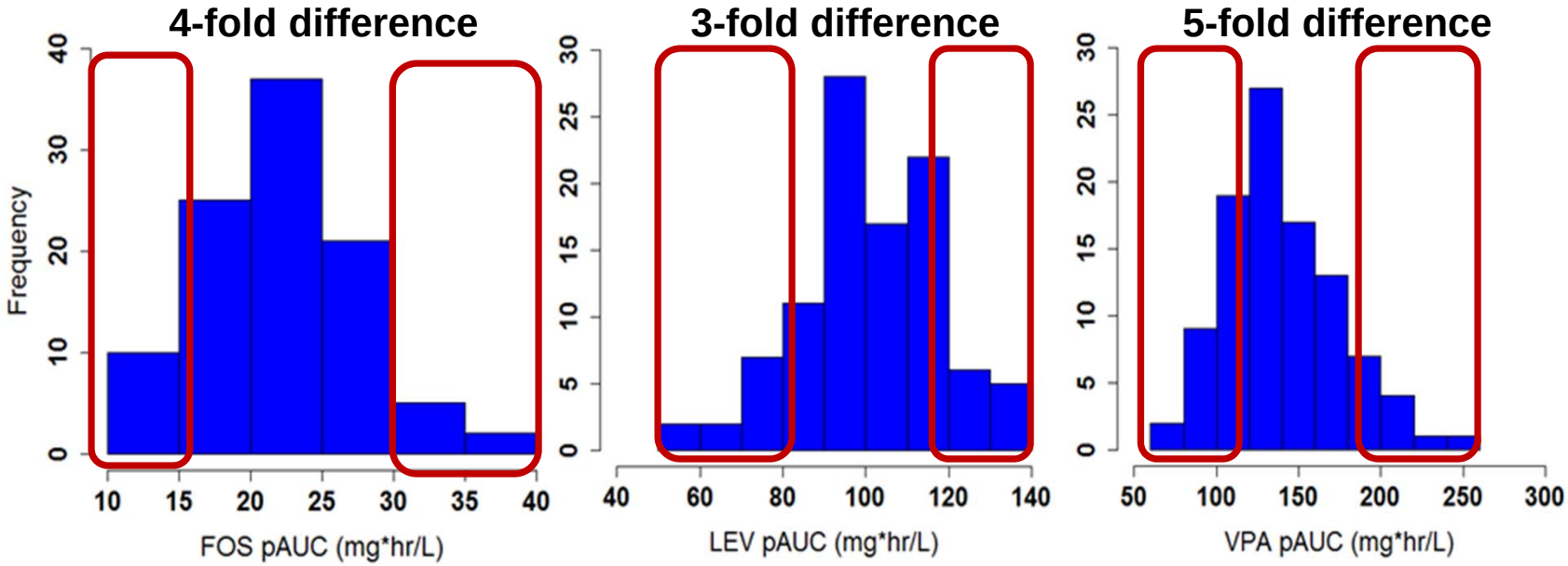
Simulations Show Wide Variability in Drug Exposure (plasma concentration) Following IV Dosing



Distributions of cumulative PHT, LEV, and VPA concentrations over 60 min (pAUC) simulated for 100 ESETT patients

Does variability in concentrations explain response?

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Specific Aim

Relate drug exposure (concentration or pAUC) with seizure cessation and the key secondary outcomes.

- ***Hypothesis 1: Patients with higher drug exposures (unbound or total plasma concentrations of FOS, LEV, and VPA) will more likely respond.***
- ***Hypothesis 2: Patients with higher drug exposures will have a higher incidence of serious adverse effects commonly associated with the study drugs.***
- ***Hypothesis 3: The relationship between drug exposure and response will differ by gender, age, weight, and/or BMI.***

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Study Overview

Population - Same as ESETT

Inclusion Criteria

- **All subjects randomized under the ESETT protocol.**
- **Able to provide blood sample(s)**

Overview of Procedures

- **Collect subject height**
- **Collect two blood samples within specified time ranges**

Sample and Data Analysis (completed at UofMN)

- **VPA (total and unbound), PHT (total and unbound) and LEV (total) concentrations measured in plasma**
- **Statistical and pharmacokinetic/pharmacodynamic analyses**

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Consenting Considerations

- **Blood collection, as part of the ESETT protocol, will occur under exception from informed consent (EFIC).**
- **If patient, parent, or other legally authorized representative (LAR) withdraws consent to continue participation from ESETT, they have also withdrawn from the PK/PD study.**

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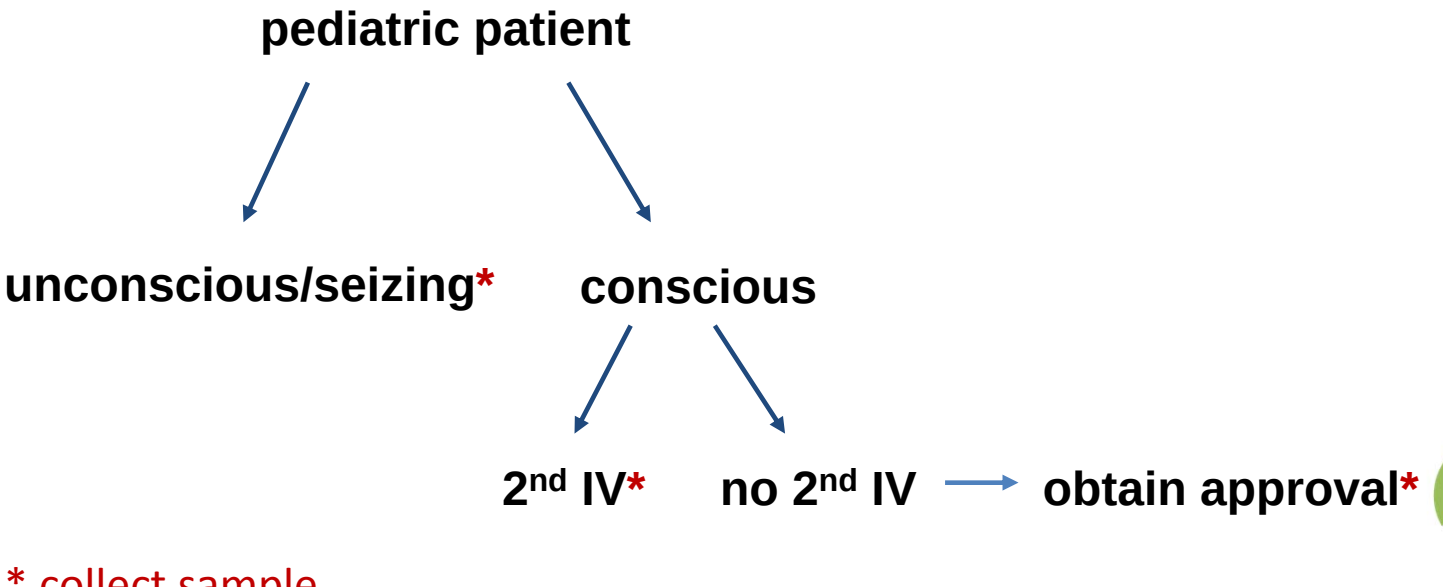
Consenting Considerations

- **For children who are conscious and do not have a second IV catheter available for blood collection, the parent or LAR should be asked if blood may be drawn by venipuncture for research purposes. If the answer is no, blood should not be collected. Further participation in ESETT should not be affected.**
  - **Even if patient, parent or other LAR informs that study team that he/she does not want blood sample(s) collected, he/she can still participate in ESETT.**



* collect sample

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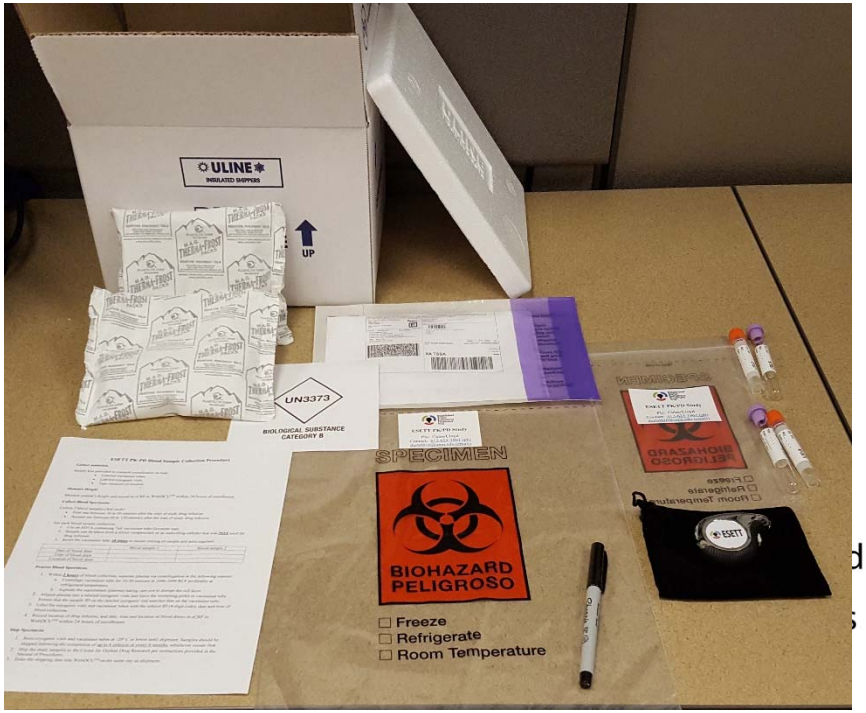
Materials

- **Supply kits will be provided to research coordinators and will include:**
  - **Labeled 7-mL lavender top vacutainer tubes (2 per subject)**
  - **Labeled 5 mL cryogenic vials (2 per subject)**
  - **Sharpie®**
  - **Tape measure**
  - **Sample collection procedures quick guide**
  - **Copy of PK eCRF**
  - **Biohazard bags**
  - **Absorbent pad**
  - **Shipping materials (cold packs, insulated boxes, biological substance label, and pre-paid FEDEX shipping labels)**



Measurement of Height

- **Measure the patient's height (using the official ESETT tape measure) and record in the medical record, eCRF worksheet, or directly in the ESETT PK eCRF.**
- **If height can't be measured, a previously recorded height or estimated height should be recorded.**

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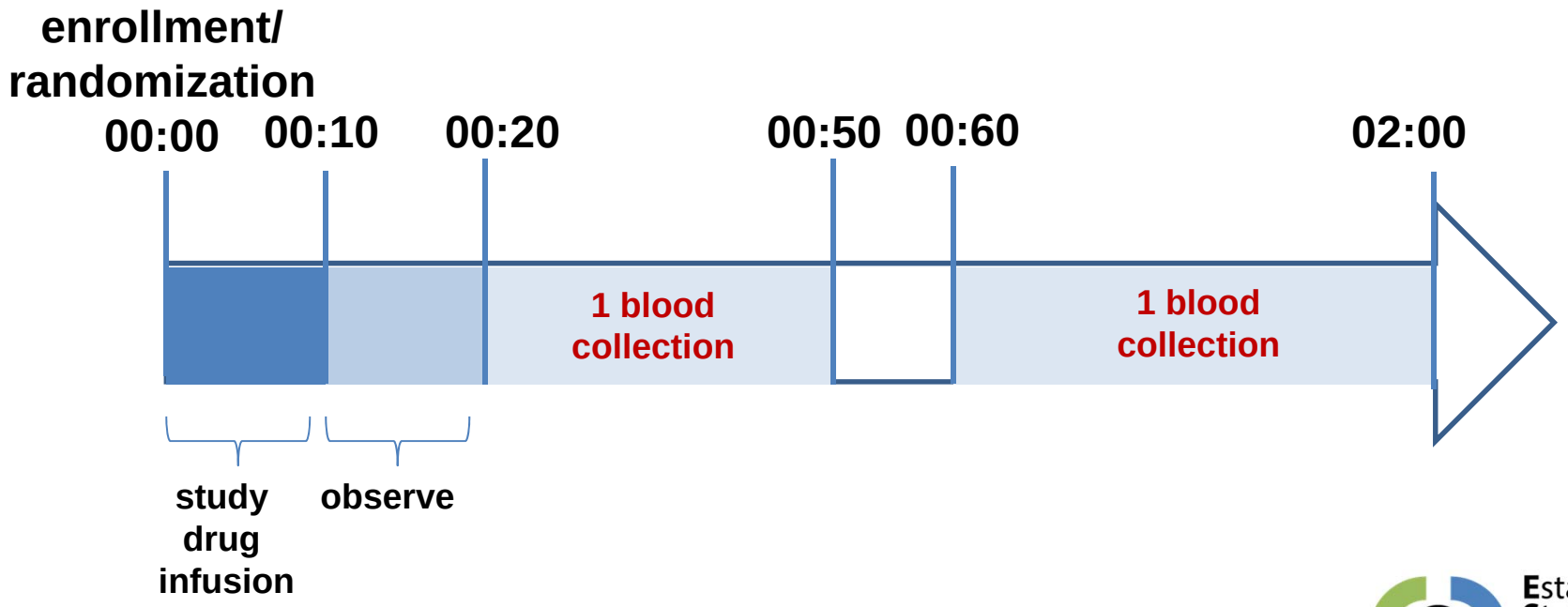
PK/PD Sample Collection Timetable

- **Collect two blood samples (2.5-3 mL/sample)**
  - **One sample between 20-50 min and a second sample between 60-120 min from the start of drug infusion**



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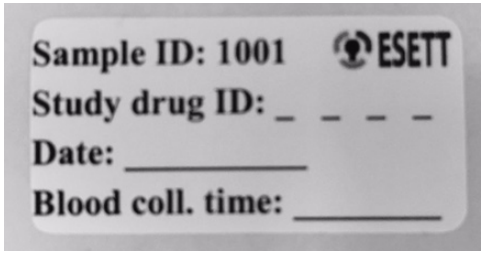
Blood Collection Procedures

- To ensure the PK samples are collected correctly mark the infusion site with an 'X' on the bandage.
- For each blood sample (2.5 - 3 mL) use an EDTA-containing vacutainer (lavender top) 7 mL tube.
- Blood can be taken from either direct venipuncture or an indwelling catheter that was **NOT** used for drug infusion.
- Invert the vacutainer tube approximately 10 times to ensure adequate mixing of blood and anticoagulant.
- Label tube with study drug ID, date, and time of blood collection
- Record the subject and sample IDs, date, time, and whether the PK sample was drawn from the study drug infusion site in the medical record, eCRF worksheet, or directly on the ESETT PK blood collection eCRF.

Blood Sample Processing

- **Within 2 hrs of the blood collection, separate plasma via centrifugation in the following manner:**
  - **Centrifuge vacutainer tube for 10 minutes at 2000 RCF preferably at refrigerated temperature.**
  - **Carefully aspirate the supernatant (plasma) taking care not to disrupt the cell layer.**
- **Aliquot plasma into a labeled cryogenic vial and leave remaining pellet in vacutainer tube.**
- **Label the cryogenic vials and vacutainer tubes with the study drug ID (4 digit code), time and date of blood collection.**



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Data Collection Procedures

- **Complete the ESETT PK Blood Collection eCRF in WebDCU™ within 5 days of enrollment. The eCRF will capture: height, the sample ID (4 digit), subject ID (4 digit), date, time, and whether the PK sample was taken from the same site as the study drug infusion for each sample.**
  - **Record any procedural deviations under Question 8. An example would be a sample processed outside of the specified time window.**
- **Samples collected outside of the sampling time windows or with smaller volumes than indicated are still useable and should be retained and shipped.**

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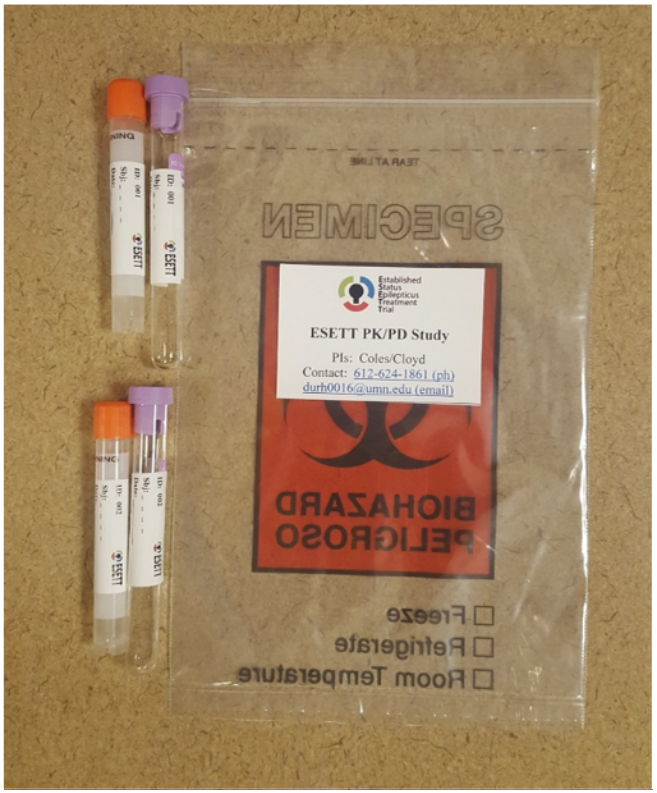
Blood Sample Storage

- **Store cryogenic vials and vacutainer tubes at -20°C or lower until shipment.**



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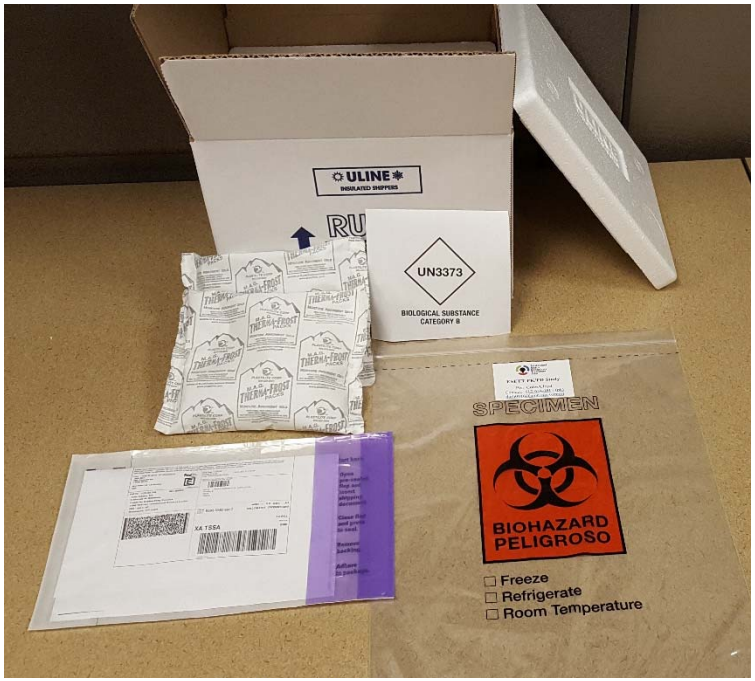
Sample Shipping

- **A subject's samples can be shipped individually or batched. If batched, the samples should be shipped following the completion of up to 4 subjects or every 6 months, whichever comes first.**
- **Ship the study samples on cold packs provided (or dry ice) to the Center for Orphan Drug Research:**

Usha Mishra, MS

University of Minnesota
Center for Orphan Drug Research
4-500 MTRF
2001 - 6th St SE
Minneapolis, MN 55455



Sample Shipping

- **Send an email notification to esett-pkpd@umich.edu at time of shipment.**
- **Enter the shipping date and FEDEX tracking number into WebDCU™.**

- **Supplies will be automatically replenished based on enrollment activities. If you are concerned about your inventory, please contact esett-pkpd@umich.edu.**

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Study Outcomes

- **Characterization of the exposure-response relationships.**
- **Provide guidance on how best to use FOS, LEV, and VPA for treatment of SE in children, adults, and elderly.**
- **Guide selection of optimal dose for future clinical trials.**

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Frequently Asked Questions

- **Can a blood sample drawn from the drug infusion site be used?**
  - **Answer: No. Studies have shown that even with multiple flushing steps, drug concentrations are very often artificially high in such samples. If blood is inadvertently drawn from the drug infusion site, please discard sample and record in the PK blood collection eCRF. While this is a procedural deviation, it is NOT a protocol deviation.**
- **Can blood drawn from a site used to deliver fluids or other study medication be used?**
  - **Answer: Yes. Blood can be drawn from any site NOT used for study drug infusion.**
- **What should I do if we collect only one blood sample?**
  - **Answer: Process and ship the sample as specified. While we expect to obtain 2 samples from most subjects, a single sample from a subset of patients will still be valuable. This is NOT a protocol deviation.**
- **What should I do if we obtain the blood sample outside of the sampling time window?**
  - **Answer: The data from this sample can still be used. Record the actual time that the sample was collected on the PK blood collection eCRF and process and ship that sample as specified. While this is a procedural deviation, it is NOT a protocol deviation.**

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Frequently Asked Questions

- **What should I do if the blood sample is centrifuged greater than 2 hrs after sample collection?**
  - **Answer: Record the procedural deviation under Question 8 of the PK blood collection eCRF. This is NOT a protocol deviation.**

- **What should I do if the volume of blood collected is less than 2.5 - 3 mL?**
  - **Answer: The sample will still be used. Process and ship the sample as specified. This is NOT a protocol deviation.**

- **What happens if I have misplaced or damaged the sample kit?**
  - **Answer: If pre-labeled vacutainer tubes or cryogenic vials are not available, you can use an EDTA-containing (lavender top) vacutainer tube for blood collection and a cryogenic vial or Eppendorf tube for the plasma sample available at your site. Tubes and vials should be labeled as specified in the Manual of Procedures.**

Contacts

- **ESETT PK/PD study team at esett-pkpd@umich.edu**
- **Lisa Coles at 612-624-1861 (office)**
- **James Cloyd at 612-624-4609 (office)**

References

- **Manual of Procedures**
- **1 page quick guide**

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