

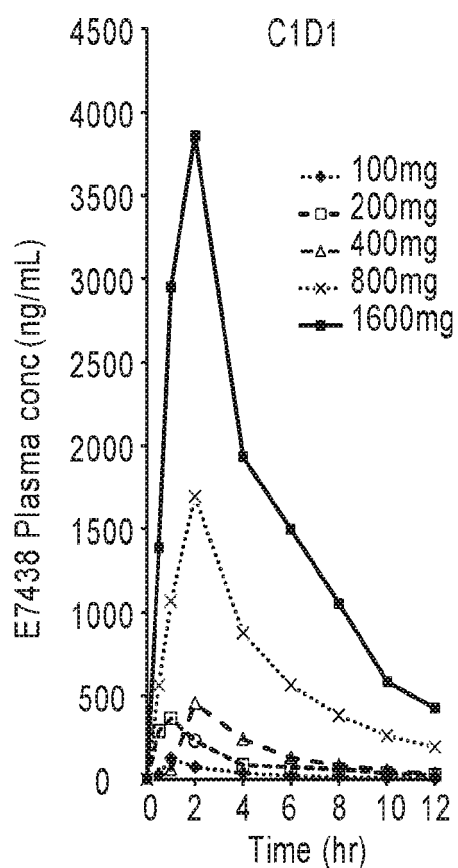


Fig. 1A

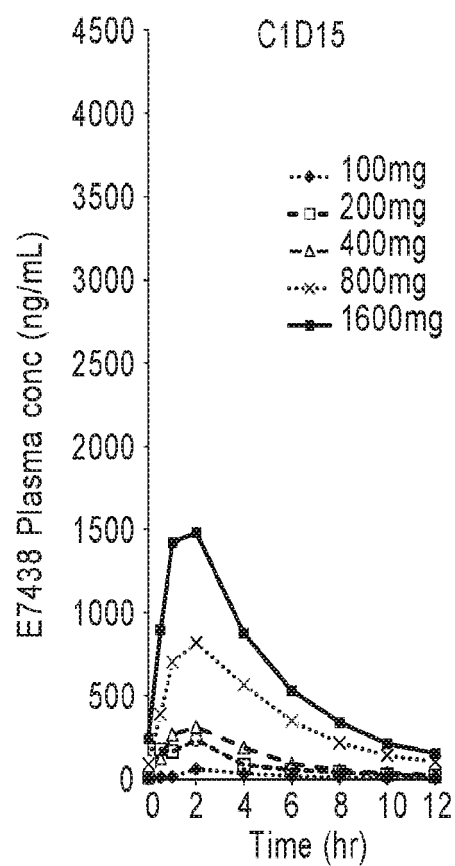


Fig. 1B

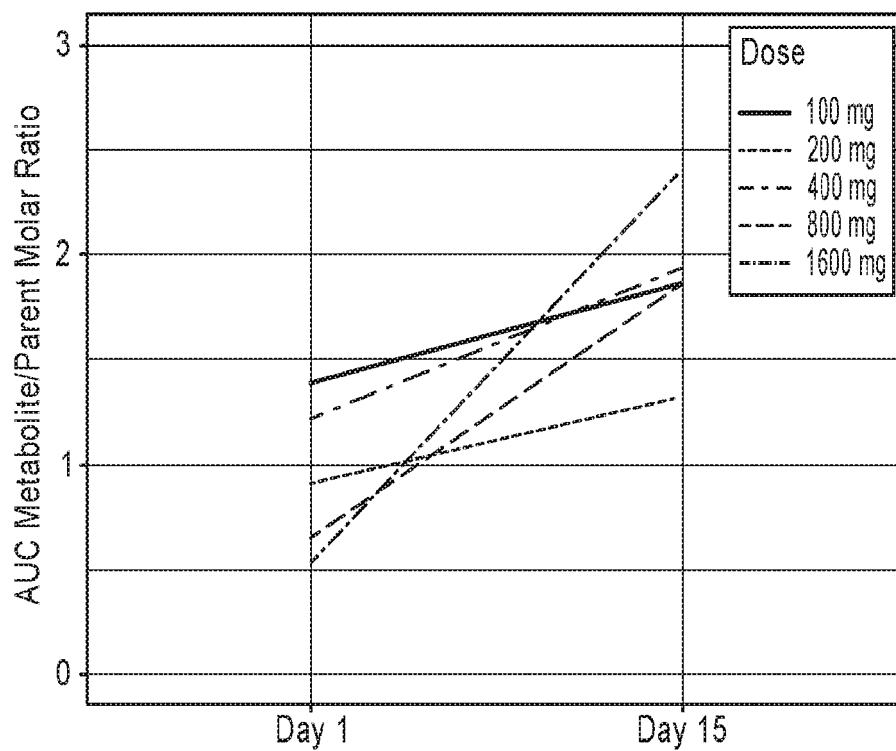


Fig. 2

2/19

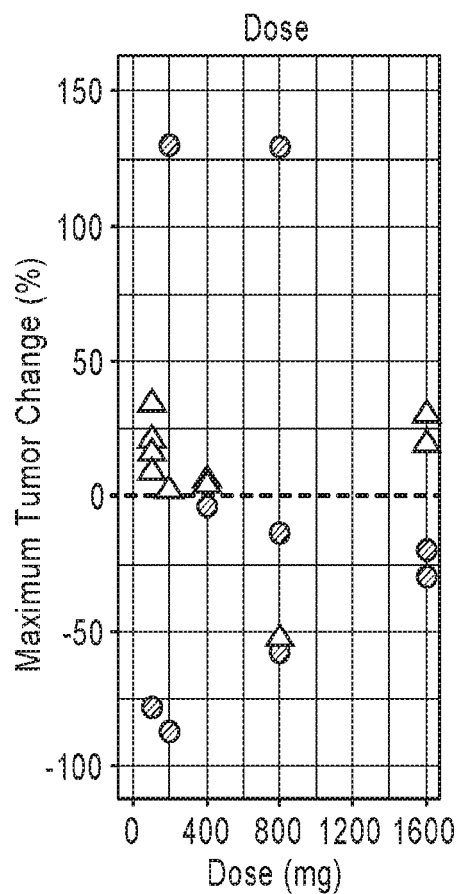


Fig. 3A

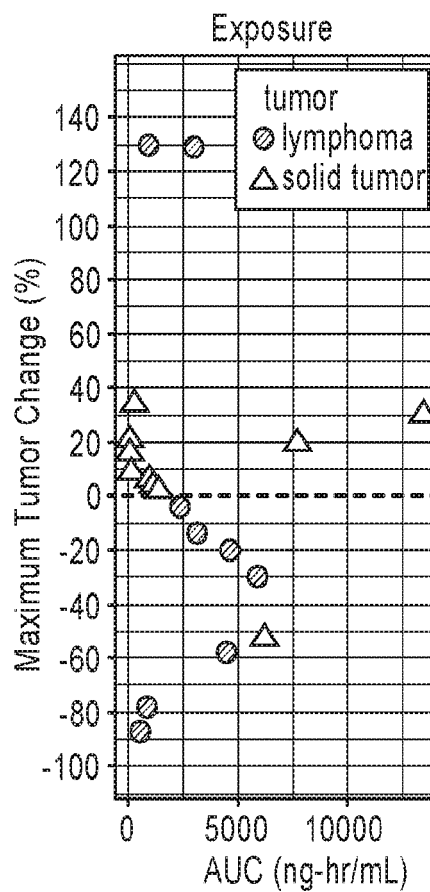


Fig. 3B

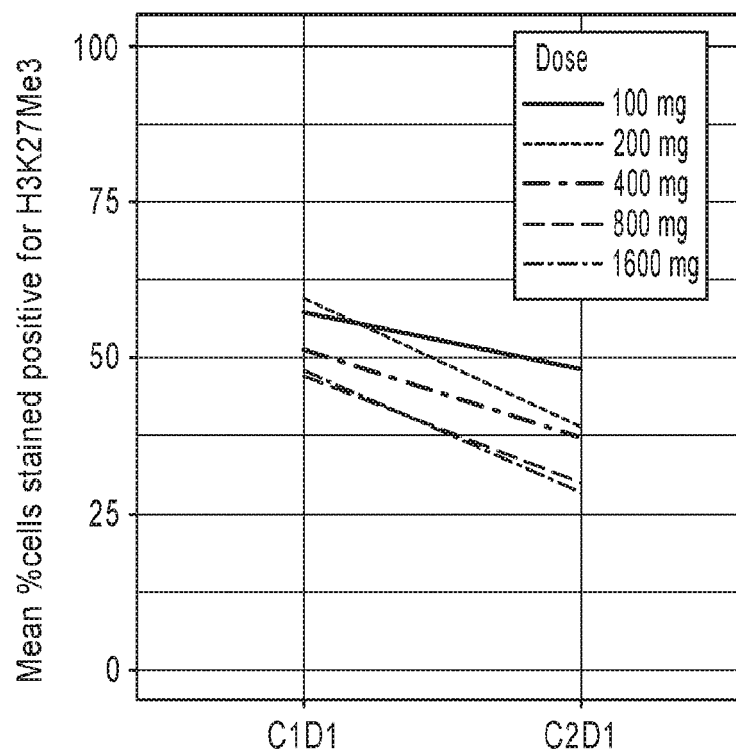


Fig. 4

3/19

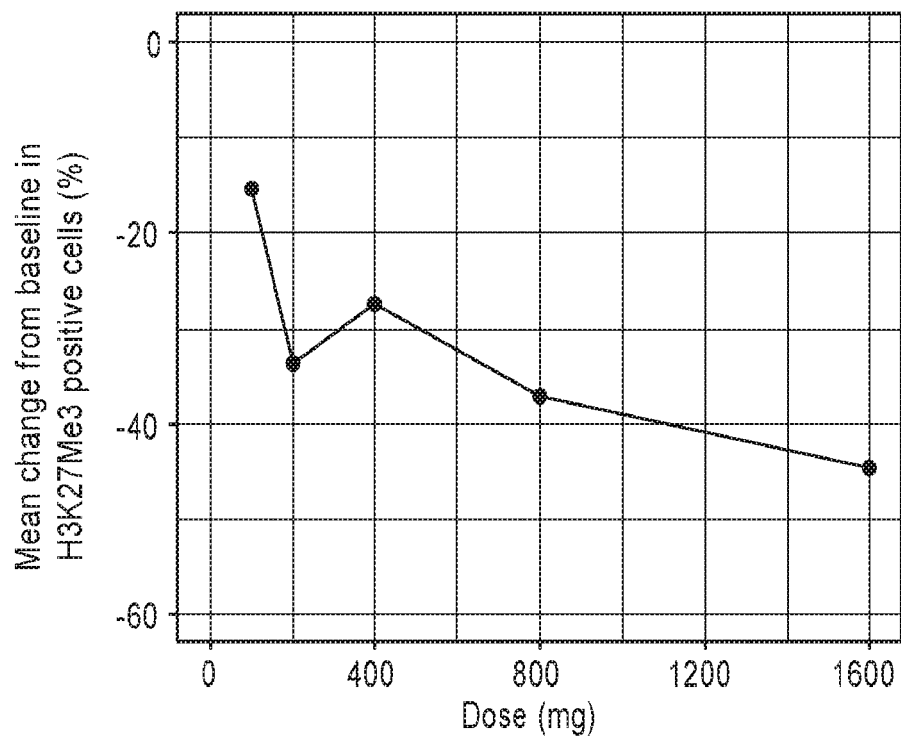


Fig. 5

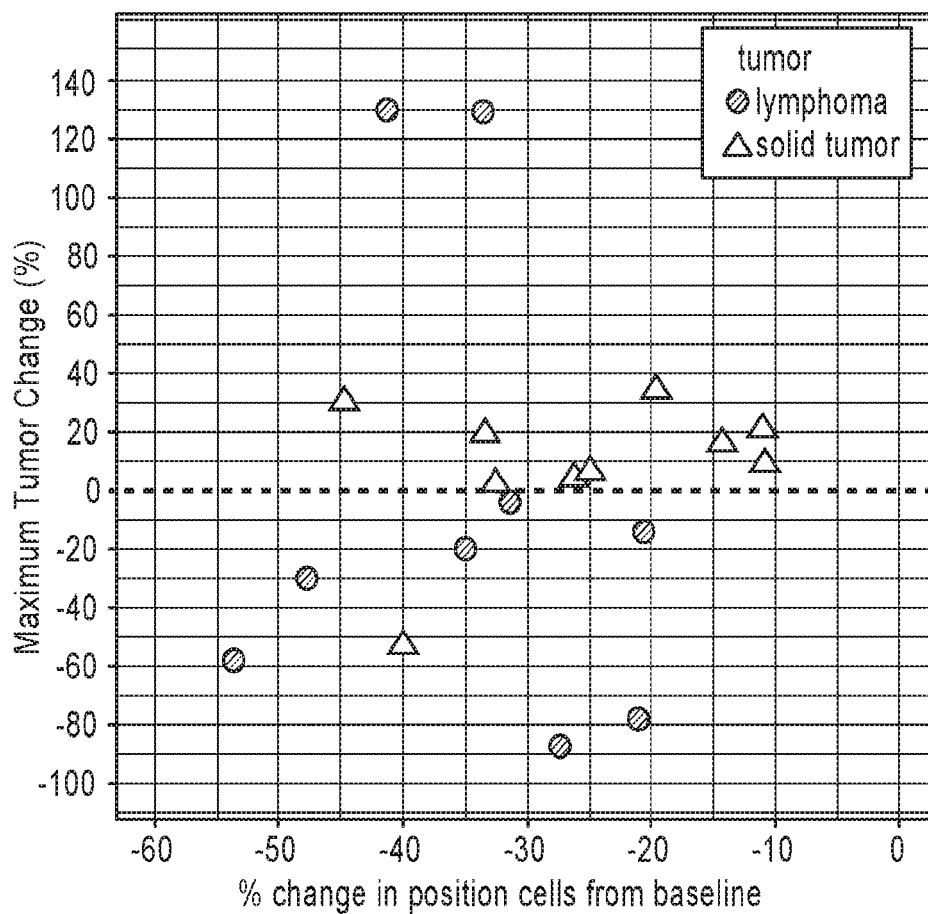


Fig. 6

4/19

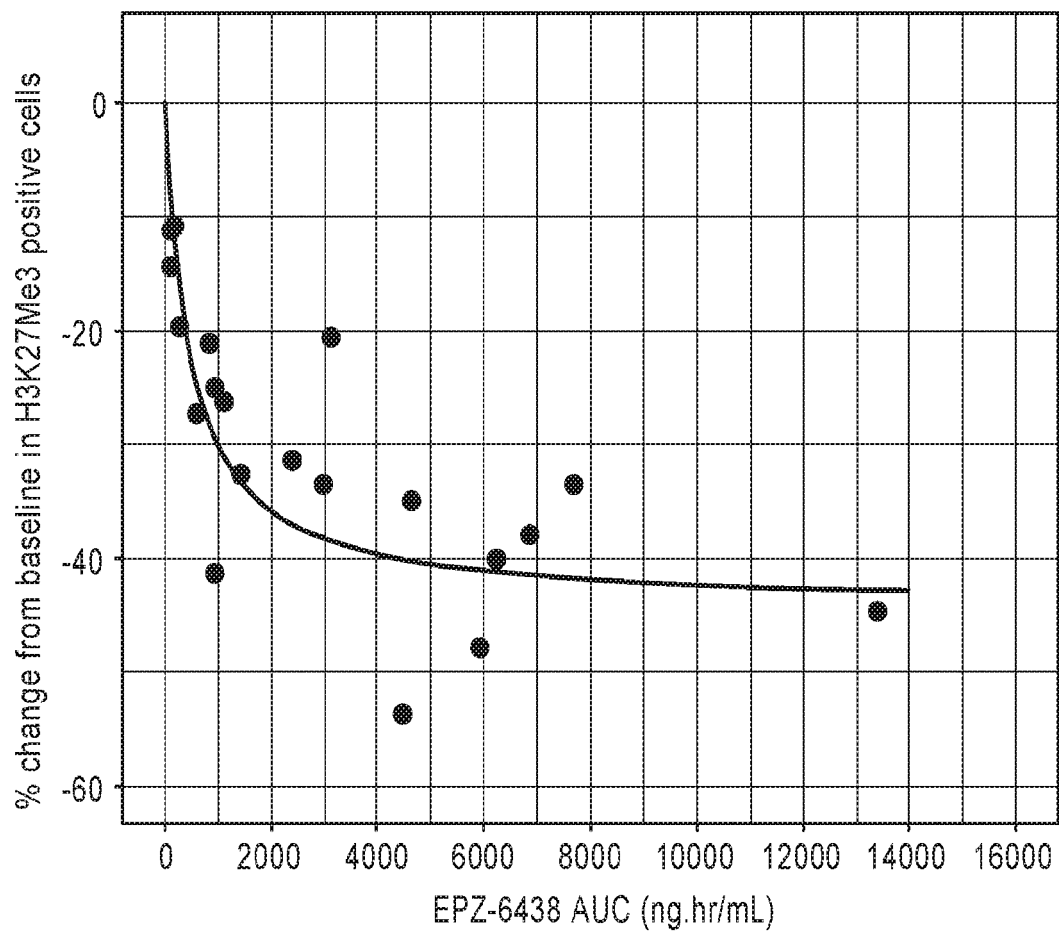


Fig. 7

5/19

	Component	Manufacturing Step
Step 1	EPZ-6438 Drug Substance Lactose Monohydrate Low-substituted Hydroxypropyl Cellulose	Mixing
Step 2	Purified Water Hydroxypropyl Cellulose	Granulation
Step 3		Drying
Step 4		Sizing
Step 5	Low-substituted Hydroxypropyl Cellulose Sodium Starch Glycolate Magnesium Stearate	Lubrication
Step 6		Tableting
Step 7	Opadry 03F45063 RED Purified Water	Film-coating

Fig. 8

6/19

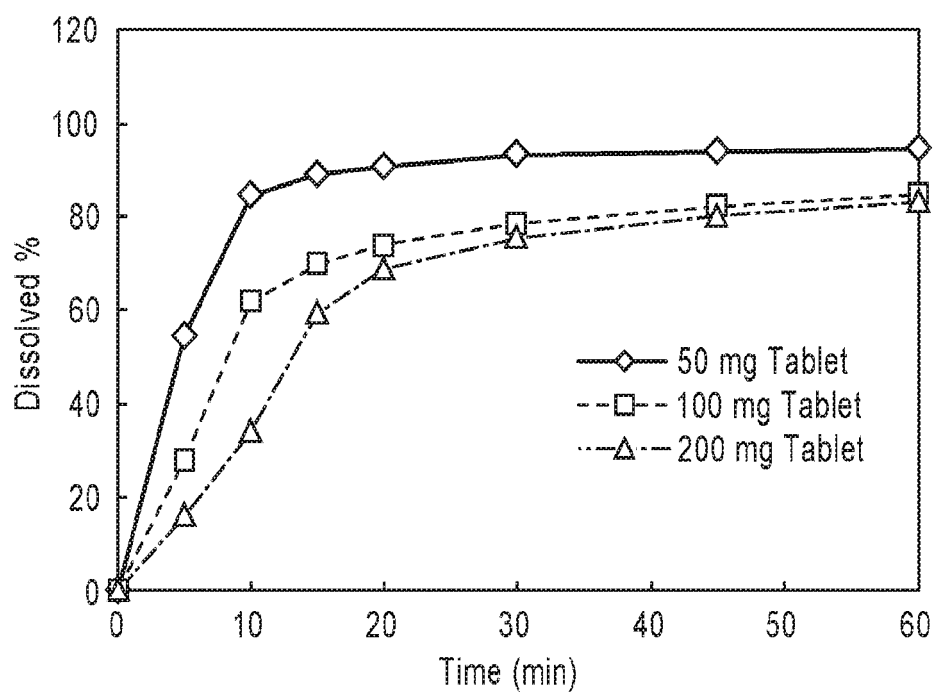


Fig. 9

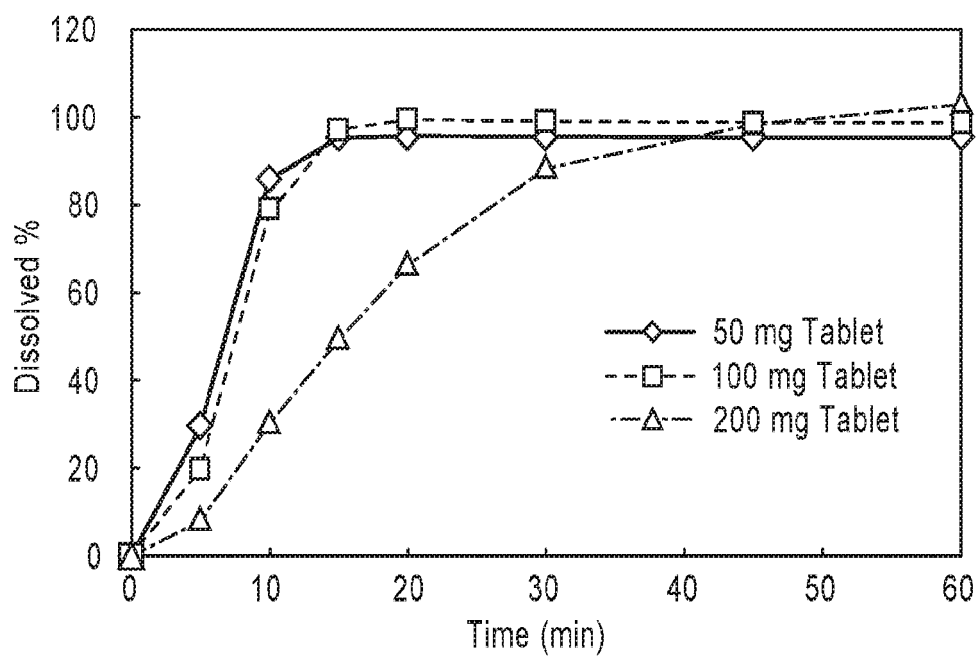


Fig. 10

7/19

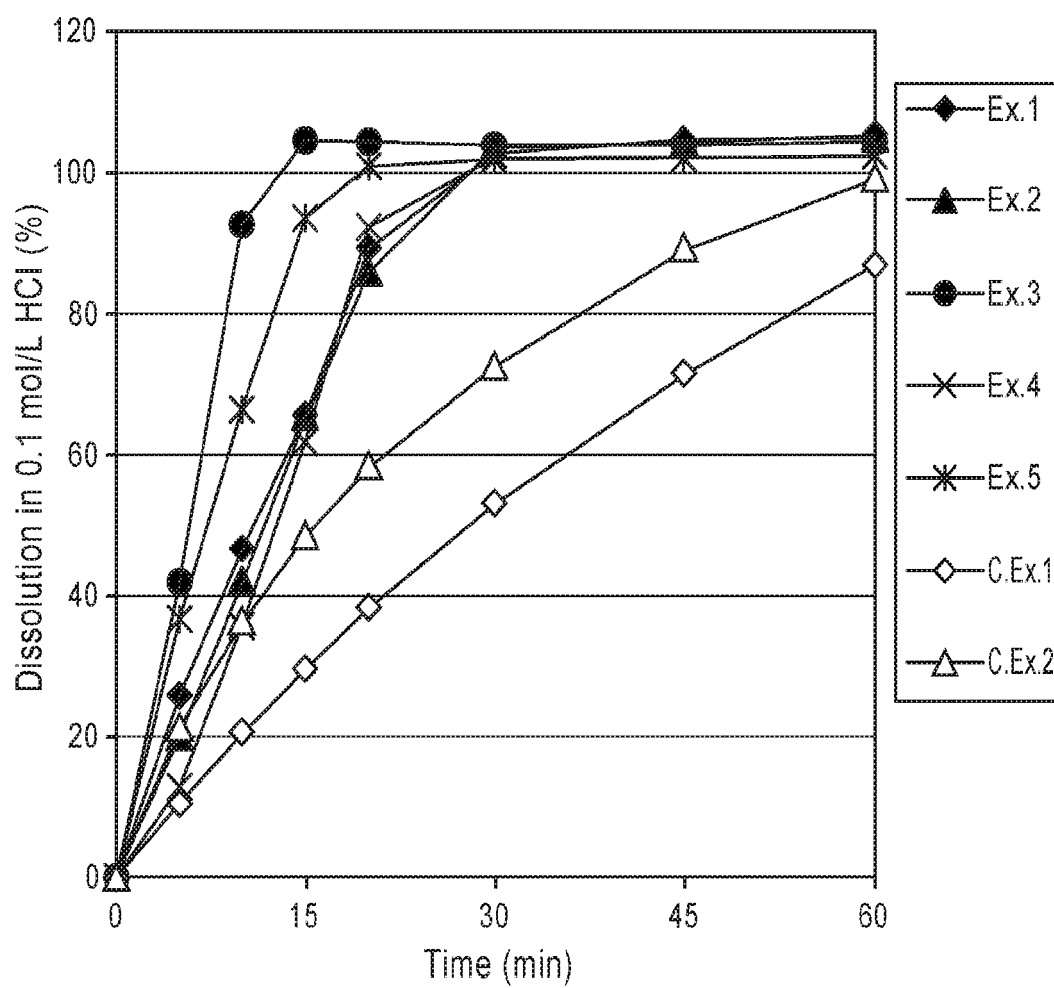


Fig. 11

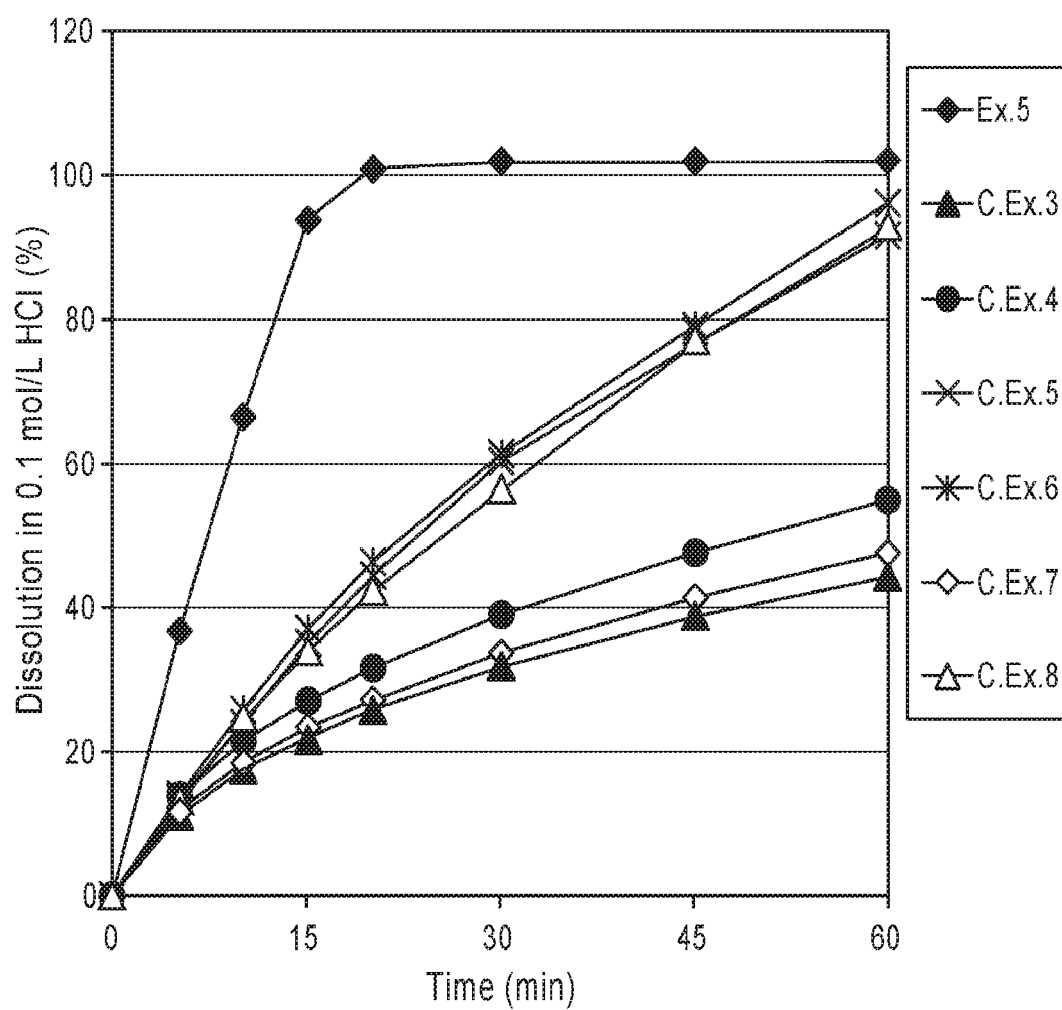


Fig. 12

9/19

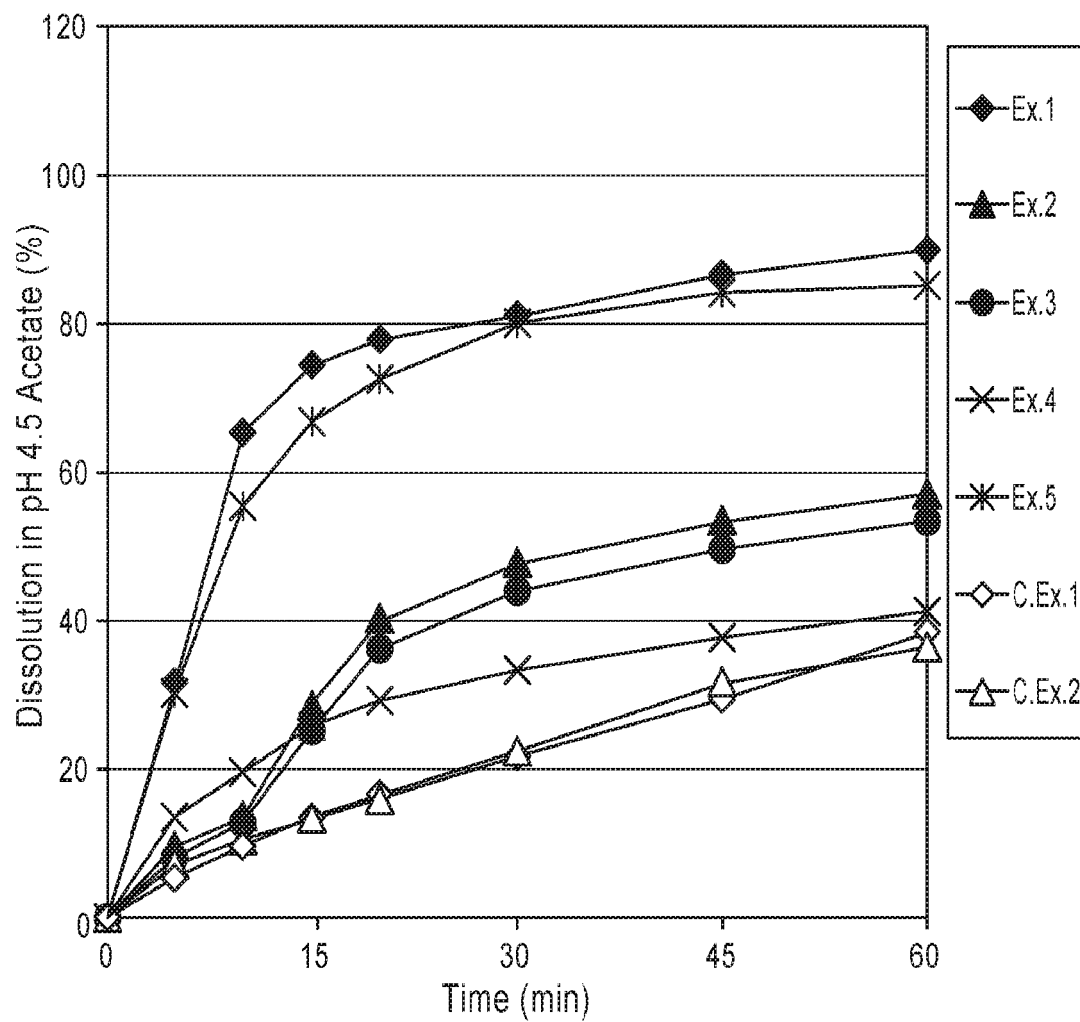


Fig. 13

10/19

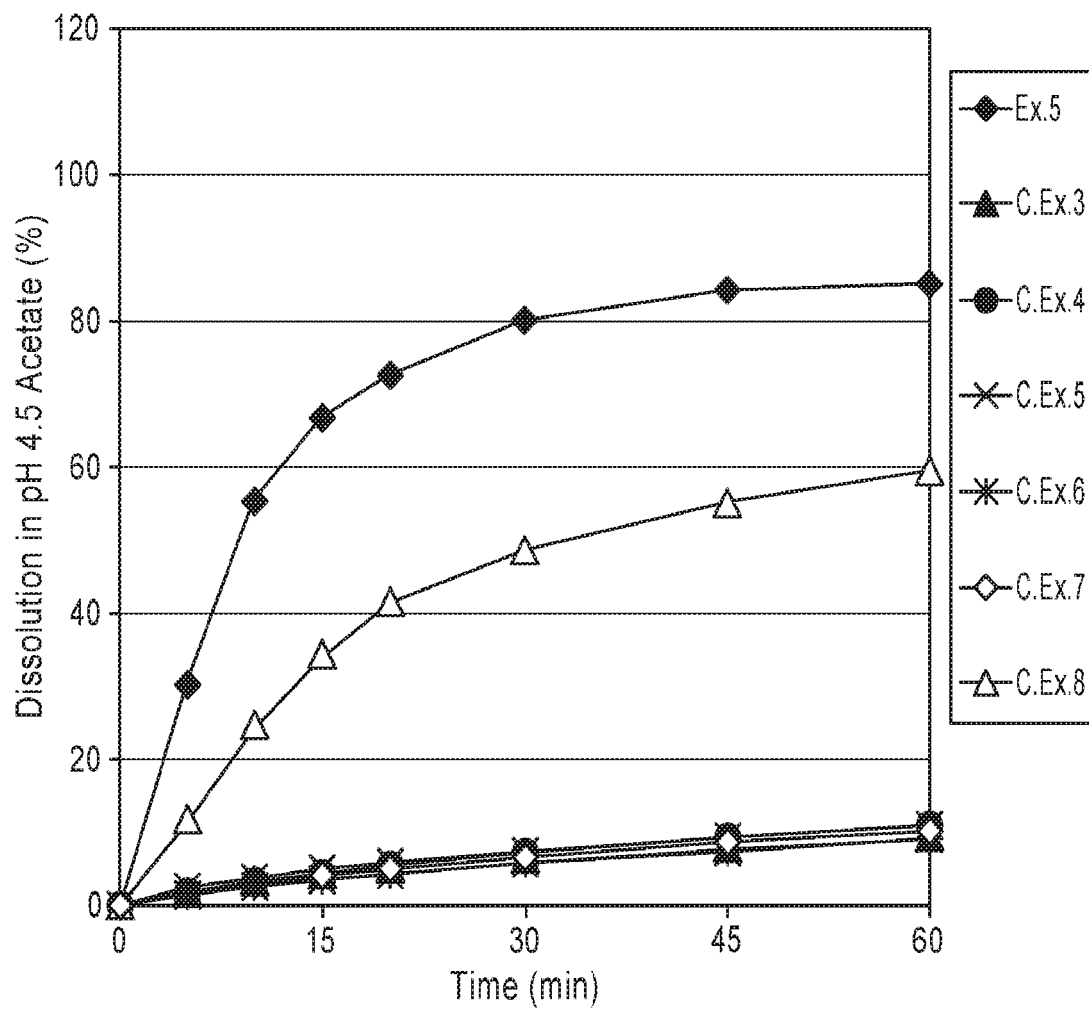
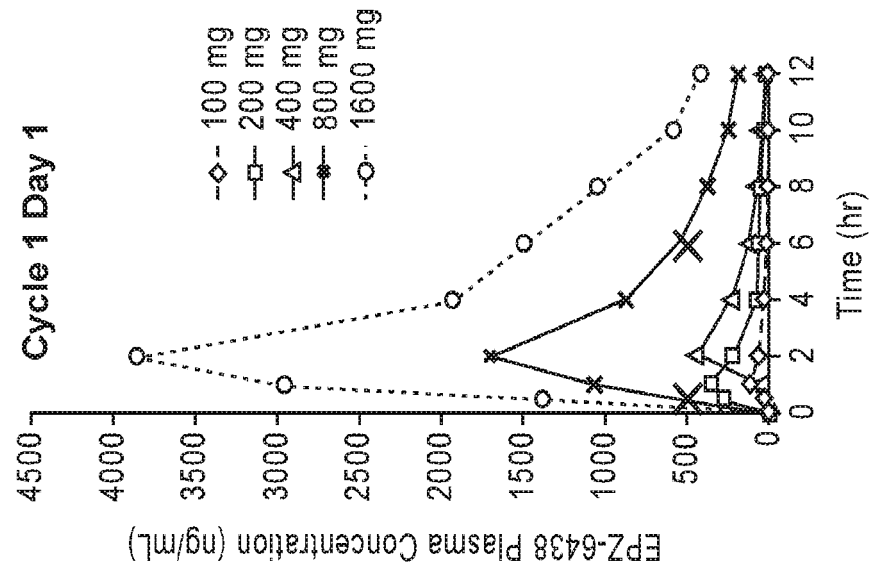
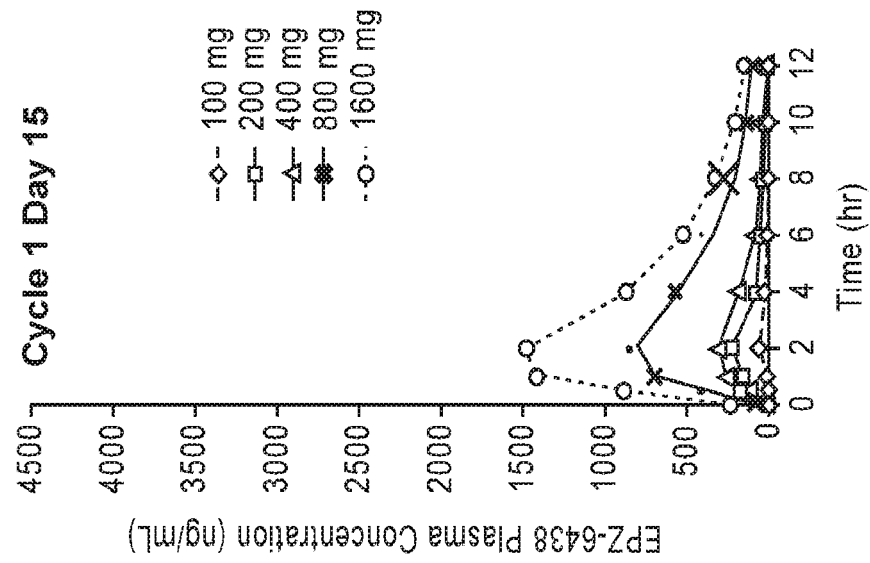


Fig. 14

11/19

Fig. 15A
EPZ-6438 Pharmacokinetics



- EPZ-6438 is rapidly absorbed and eliminated ($t_{1/2} \sim 3-6$ hours)
 - EPZ-6438 exposure is greater than dose-proportional, and highly variable (% CV: 32-95%)
 - Decrease in EPZ-6438 exposure upon multiple-dosing is associated with increase in metabolite formation
- CV, coefficient of variation.

12/19

Fig. 15B

EPZ-6438 Pharmacodynamics in Skin

**Example of biological activity
(histone H3K27Me3 inhibition
demonstrated by IHC)**

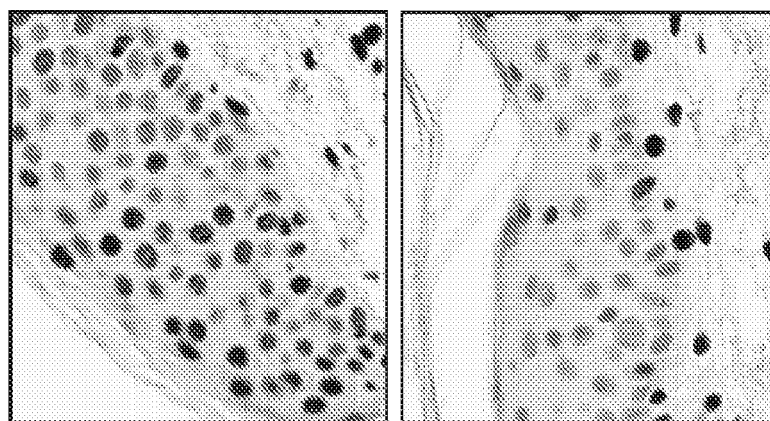
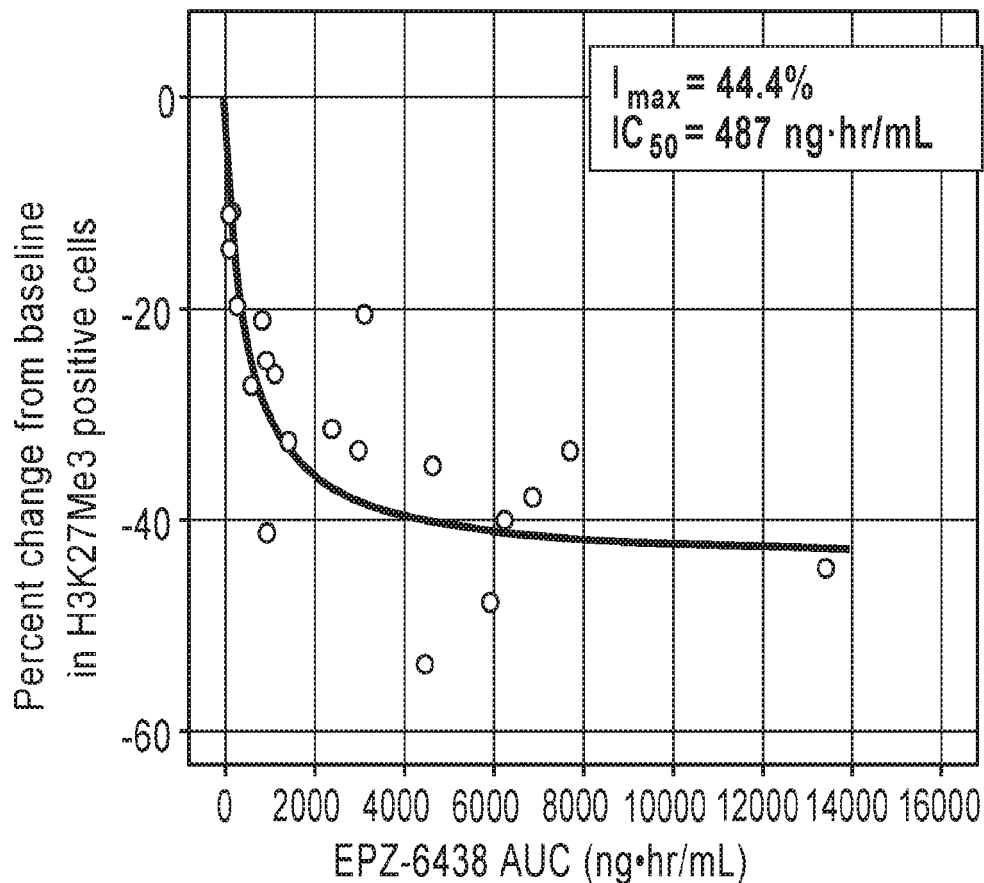
**Baseline****Cycle 2 Day1**

Fig. 15C

EPZ-6438 Pharmacodynamics in Skin

**Correlation between inhibition
of histone methylation
and exposure**



Maximal inhibition ($IC_{90} = 4421 \text{ ng}\cdot\text{hr/mL}$) is predicted
at the exposure observed for the 800 mg dose
($AUC_{\text{day 15}} = 4553 \text{ ng}\cdot\text{hr/mL}$)

Fig. 16A

Advanced Image Analysis of H3K27 Trimethylation in Skin from Subjects
Dosed with the EZH2 Inhibitor Tazemetostat

Results

Pre-clinical H3K27me3 PD studies

EZH2 inhibition leads to a decrease of H3K27me3 in skin epidermis from rats treated with increasing doses of tazemetostat for 28 days.

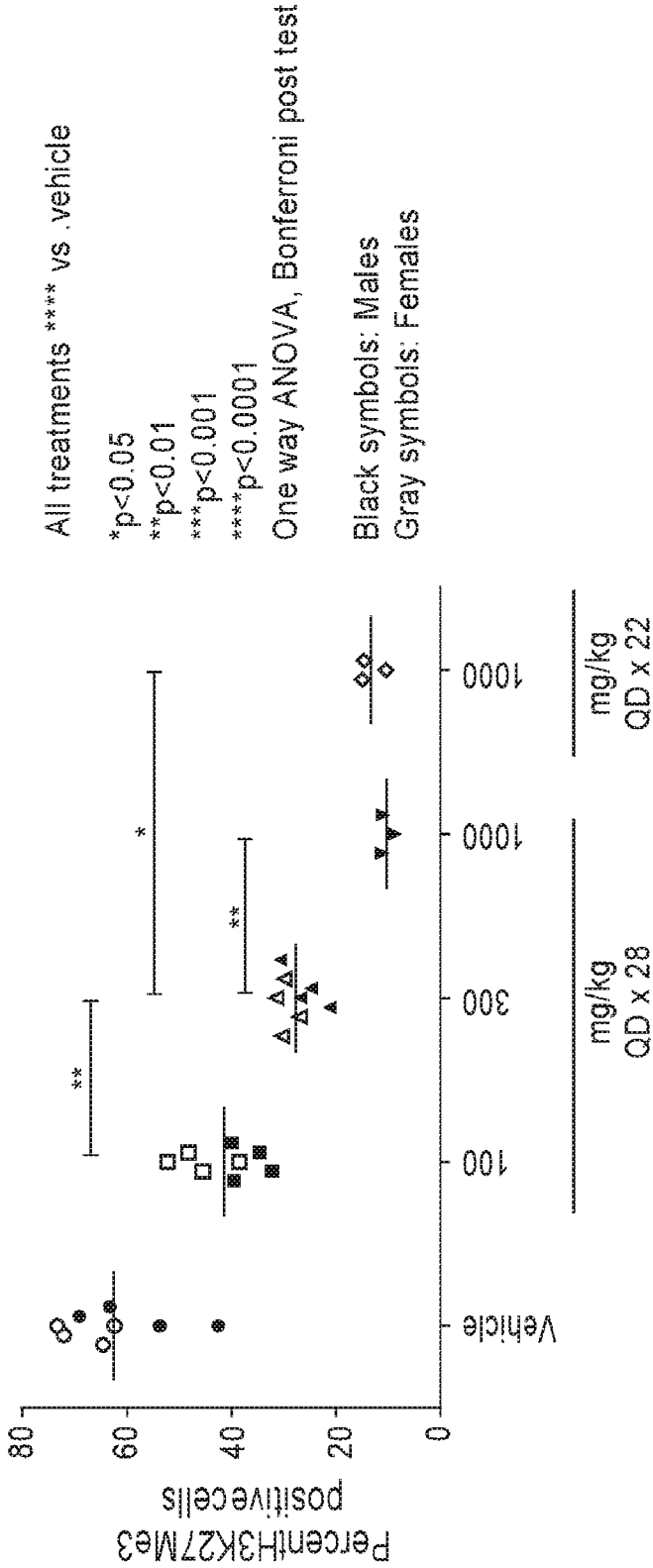


Fig. 16B
Advanced Image Analysis of H3K27 Trimethylation in Skin from Subjects
Dosed with the EZH2 Inhibitor Tazemetostat

Results

Relationship between steady-state systemic exposure and H3K27me3 mark in skin epidermis of preclinical species.

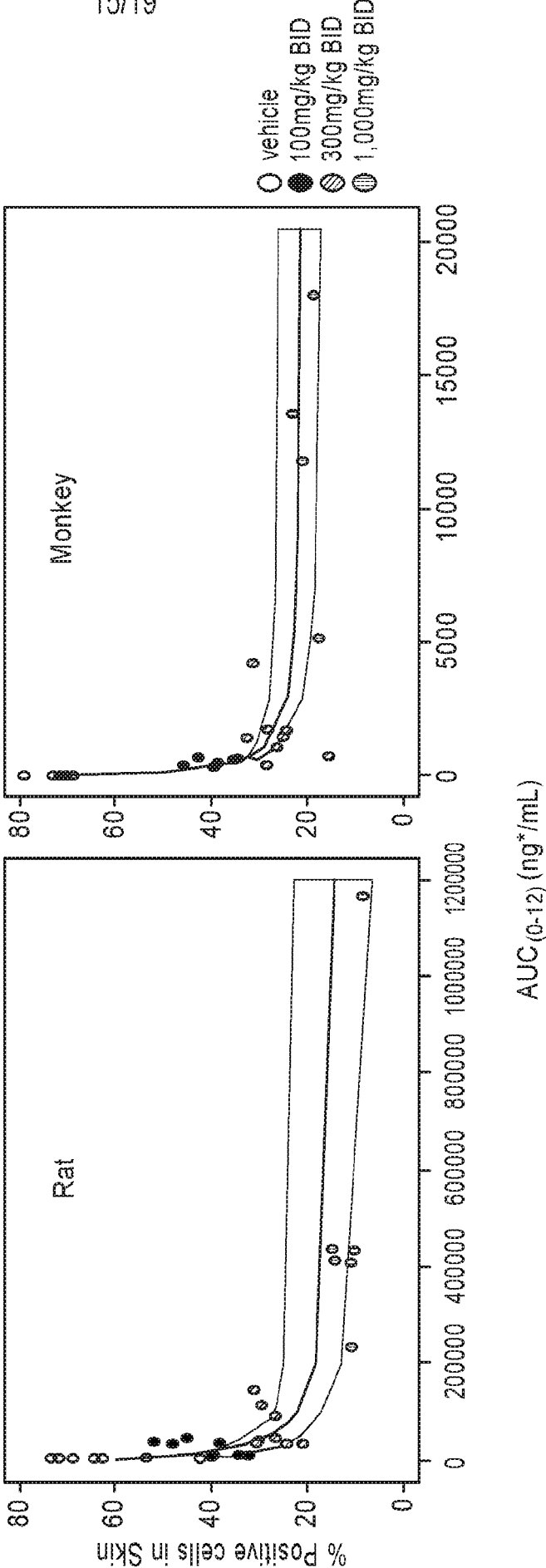


Fig. 16C

Advanced Image Analysis of H3K27 Trimethylation in Skin from Subjects
Dosed with the EZH2 Inhibitor Tazemetostat

Results

Overview of Human Epidermal Layers

An H&E image from skin delineating the multiple layers/stratum: (a) full epidermal layer, (b) basale, the single cell layer at the base of the epidermis and (c) spinosum.

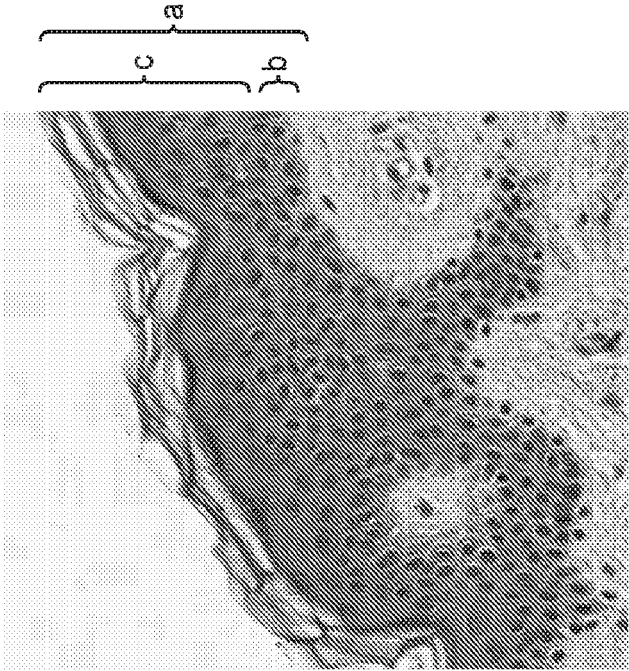


Fig. 16D

Advanced Image Analysis of H3K27 Trimethylation in Skin from Subjects
Dosed with the EZH2 Inhibitor Tazemetostat

Results

Clinical H3K27me3 PD

Skin biopsies at baseline exhibit uniform nuclear H3K27me3 throughout the epidermis. Post dose samples collected at four weeks show decreased staining in the stratum spinosum while the stratum basale appears minimally effected.

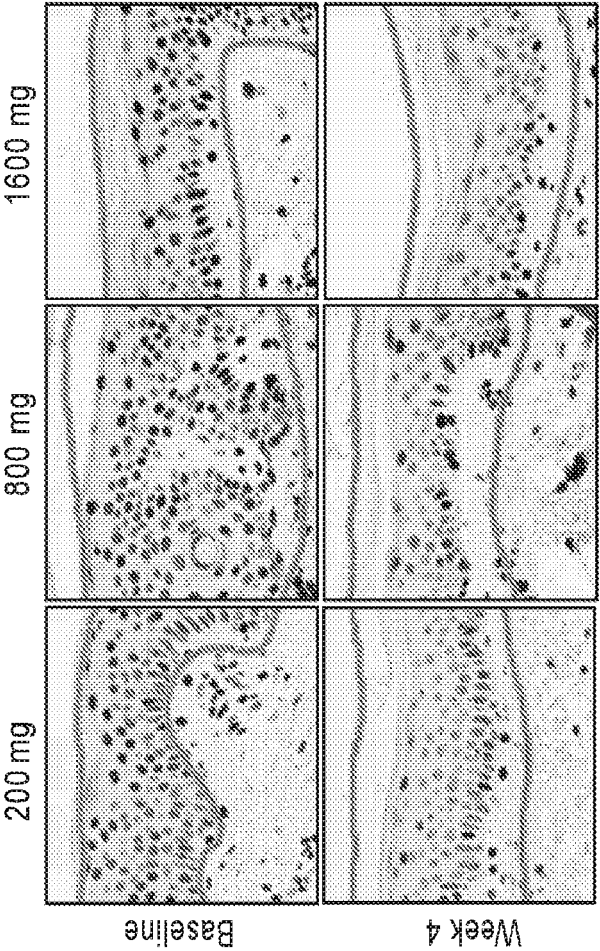


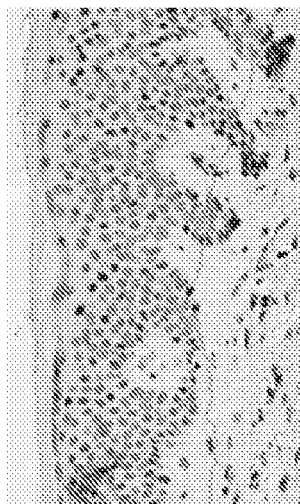
Fig. 16E

Advanced Image Analysis of H3K27 Trimethylation in Skin from Subjects
Dosed with the EZH2 Inhibitor Tazemetostat

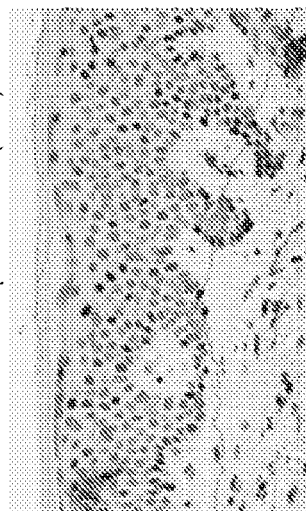
Results

Image Analysis

Image analysis identifies H3K27me3 positive (dark blue outline) and negative (aqua outlines) nuclei within the epidermal region of human skin.



Nuclei outlined in green represent the segregated basale cells from the strata spinosum (red).



19/19

Fig. 16F

Advanced Image Analysis of H3K27 Trimethylation in Skin from Subjects
Dosed with the EZH2 Inhibitor Tazemetostat

Results**Human PK/PD Relationship Analysis**

Fractional change from baseline when comparing both dosage at Day 28 (left) and AUC (right) exhibits an improved correlation of H3K27me3 in the stratum spinosum vs. the epidermis.

