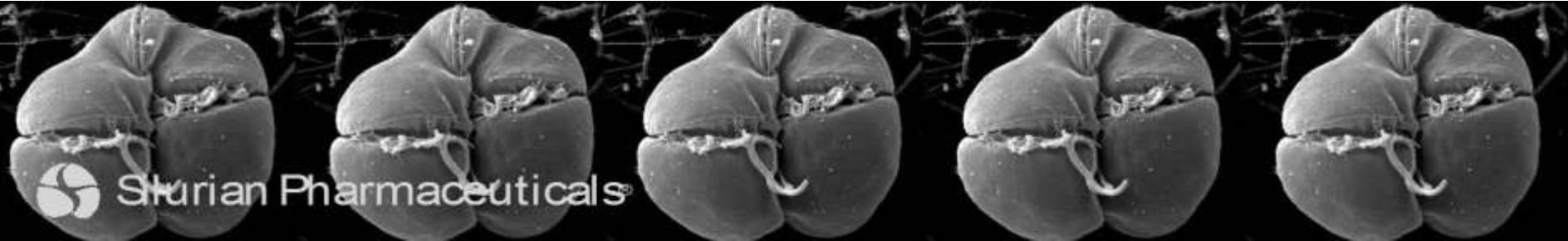




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ISAAC COHEN, O.M.D., PH.D.
NOVEMBER 6, 2015



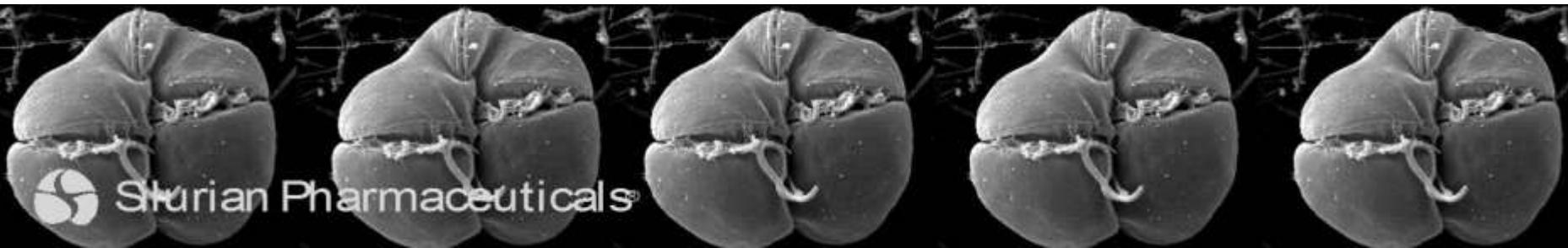
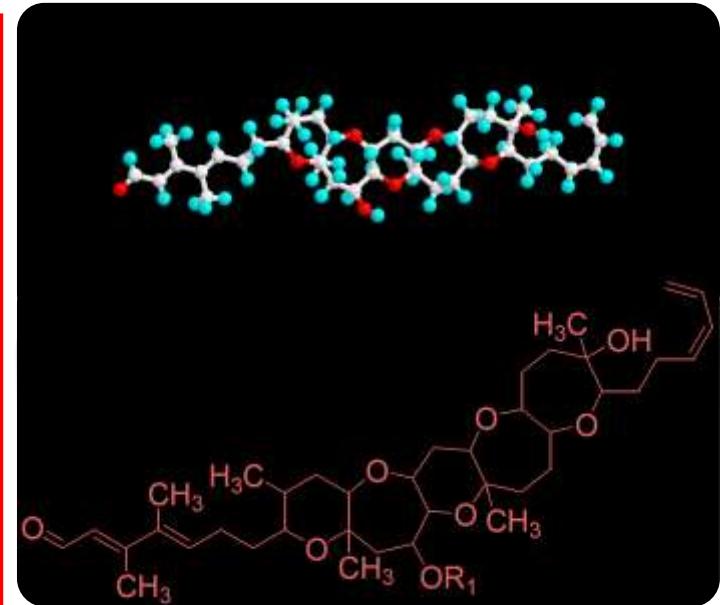
DISCLOSURE

PRESIDENT AND CEO OF SILURIAN PHARMACEUTICALS
SHARE HOLDER



KARENIA BREVIS & BREVENAL FOR LUNG DISEASES

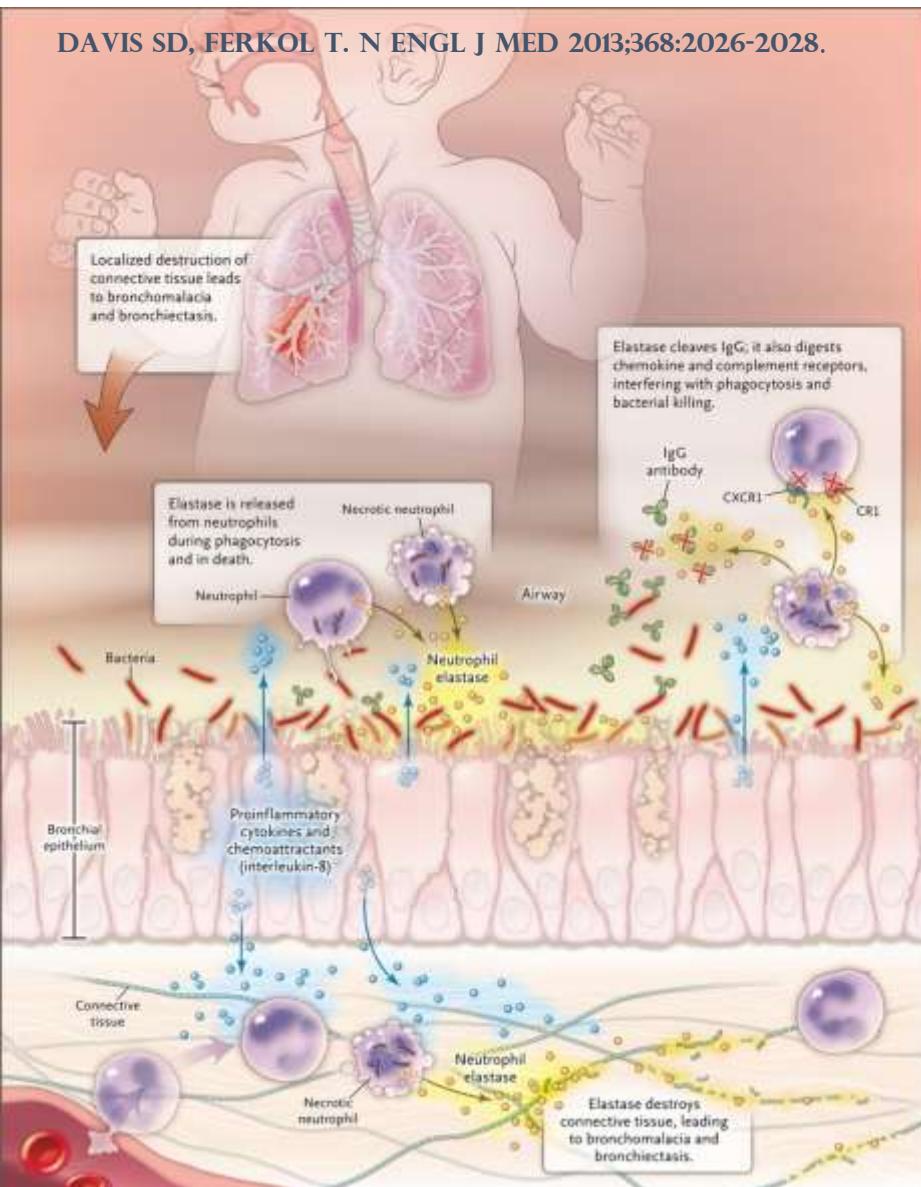
- *KARENIA BREVIS* IS A MARINE MICRO-ORGANISM
- *K. BREVIS* PRODUCES NOVEL POLYKETIDE COMPOUNDS
- BREVENAL DISCOVERED IN ALL *KARENIA BREVIS* ISOLATES
- BREVENAL IS AN INHALED COMPOUND FOR THE RELIEF OF BRONCHOCONSTRICTION AND MUCUS CLEARANCE



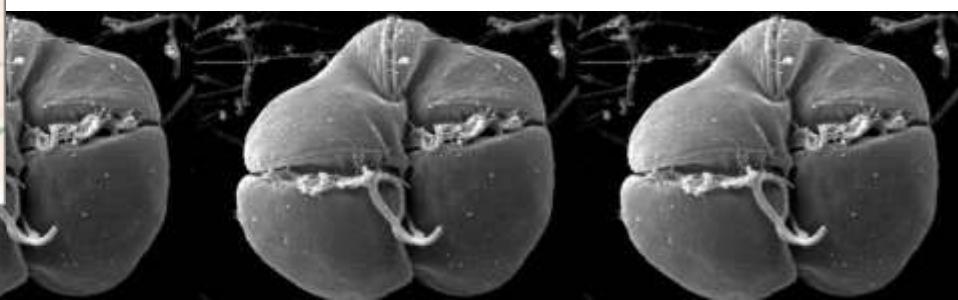
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CYSTIC FIBROSIS & NEUTROPHIL ELASTASE

DAVIS SD, FERKOL T. N ENGL J MED 2013;368:2026-2028.



- NEUTROPHIL PROTEASES ARE CRITICAL FOR KILLING BACTERIA IN THE AIRWAYS
- ACCUMULATION OF NEUTROPHIL ELASTASE (NE) DEGRADES STRUCTURAL PROTEINS IN AIRWAYS
- THIS LEADS TO BRONCHIECTASIS AND BRONCHOMALACIA
- NE STIMULATES INFLAMMATORY RESPONSE FROM AIRWAYS EPITHELIUM
- NE INTERFERES WITH BACTERIAL CLEARANCE, IMPAIRING CILIARY FUNCTION AND IGG
- NE CLEAVES CHEMOKINE AND



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BREVENAL INHIBITS NEUTROPHIL ELASTASE INDUCED BRONCHOCONSTRICTION *IN VIVO*

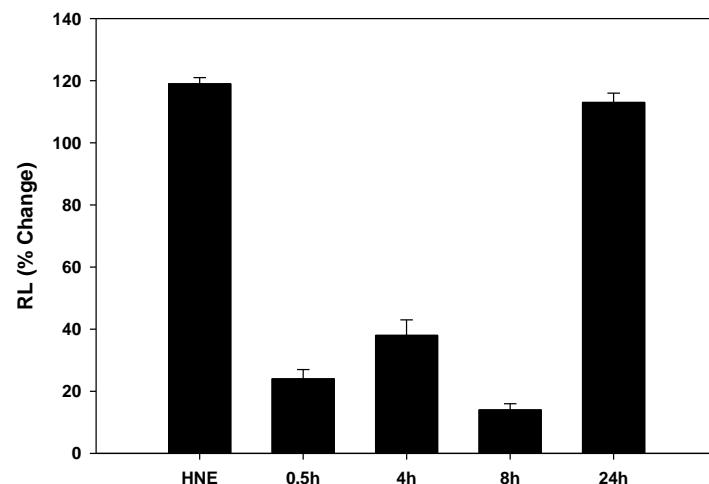
BREVENAL IS EFFECTIVE >8HRS FOLLOWING HNE INDUCED BRONCHOCONSTRICTION

7% HYPERTONIC SALINE HAS MILD EFFECT

STEROIDS (BUDESONIDE) HAS NO EFFECT ON HNE INDUCED BRONCHOCONSTRICTION

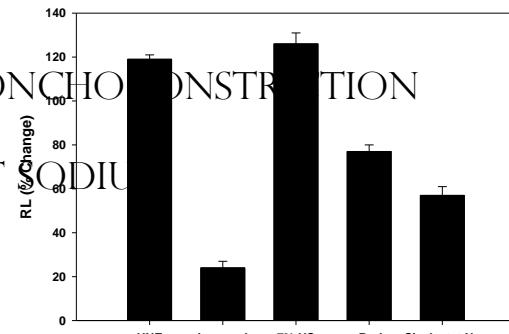
BREVENAL IS SUPERIOR TO THE ELASTASE INHIBITOR SIVELESTAT SODIUM

Time course of 50 ug/mL brevenal on HNE-induced bronchoconstriction



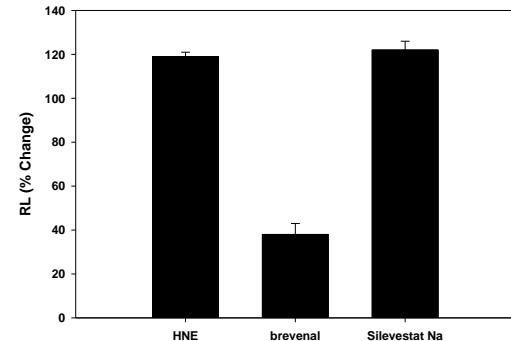
Values are mean \pm se for 3-9 sheep. A single treatment (100 breaths of 50 ug/mL brevenal) loses its effect against HNE between 8 and 24h.

Effect of different agents on HNE-induced bronchoconstriction

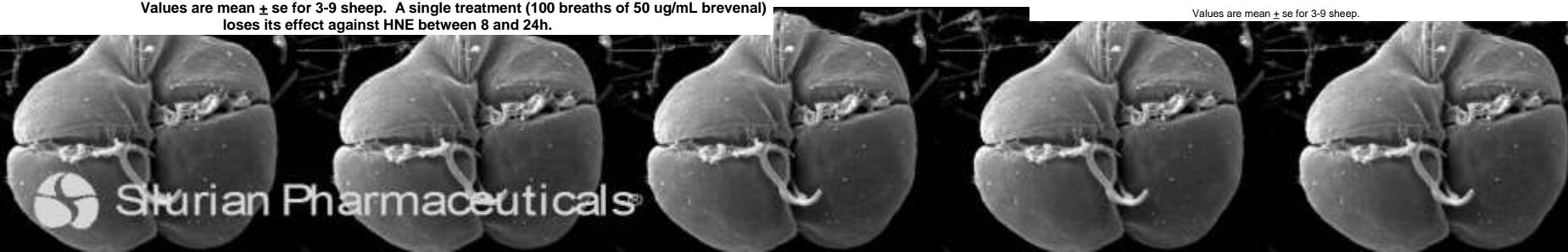


Values are mean \pm se for 6-9 sheep. Agents were given as aerosols 30 min -1h before HNE challenge. Brevenal (100 breaths 50 ug/mL), Bud (budesonide 1 mg/3 mL), Sivelestat Sodium (10 mg mL).

Comparison of the HNE-inhibitor Sivelestat Sodium and brevenal on HNE-induced bronchoconstriction when given 4h before HNE challenge



Values are mean \pm se for 3-9 sheep.



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HNE CAUSED A SIGNIFICANT INCREASE IN TOTAL CELLS, NEUTROPHILS AND MACROPHAGES.

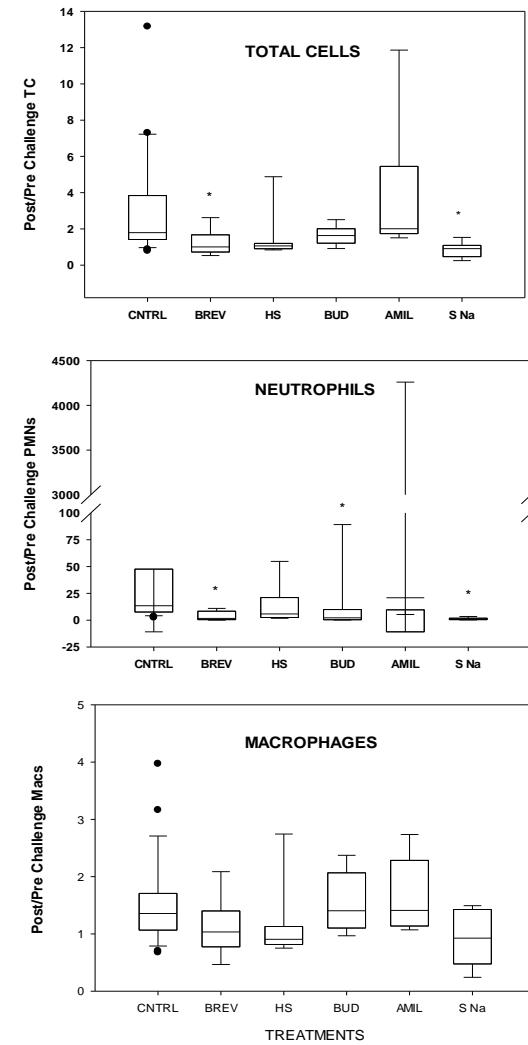
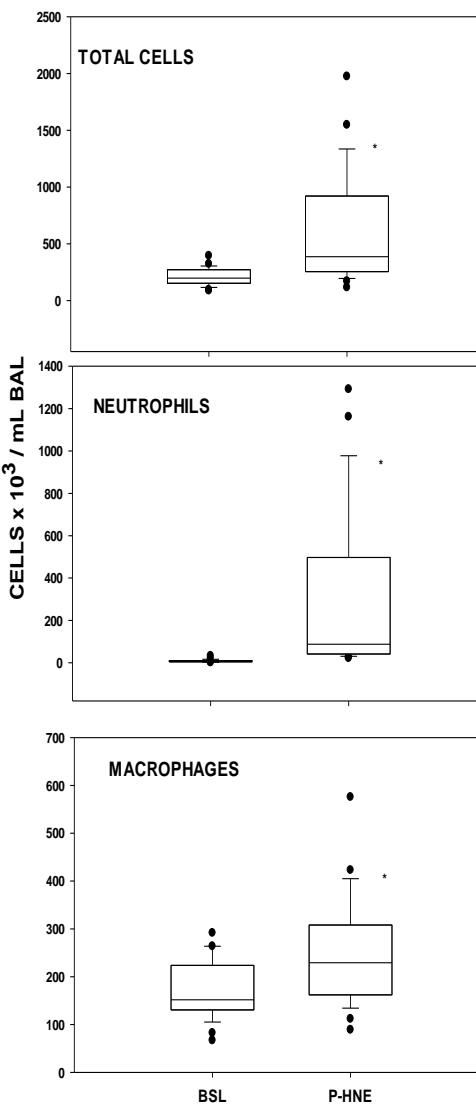
ONLY BREVENAL AND S NA REDUCED THE TOTAL CELL RESPONSE.

BREVENAL, BUD AND S NA REDUCED THE NEUTROPHIL RESPONSE.

THERE WERE NO DIFFERENCES IN THE MACROPHAGE RESPONSE.

MEDIAN VALUES WITHIN BOX, LOWER BOX LIMIT 25%, UPPER BOX LIMIT 75%, UPPER WISKER 90%, LOWER WISKER 10%.

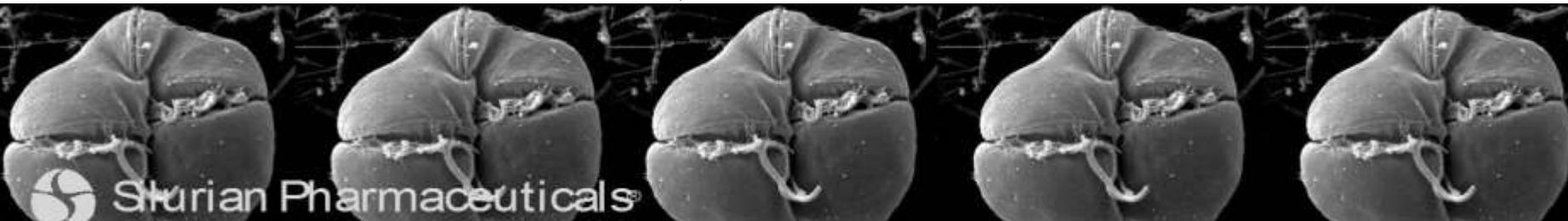
DATA POINTS OUTSIDE THESE RANGES ARE ALSO PLOTTED *
 $P < 0.05$ VS BSL ** CNTRL



BREVENAL PREVENTS WBC AND NEUTROPHIL INFILTRATION IN AIRWAYS

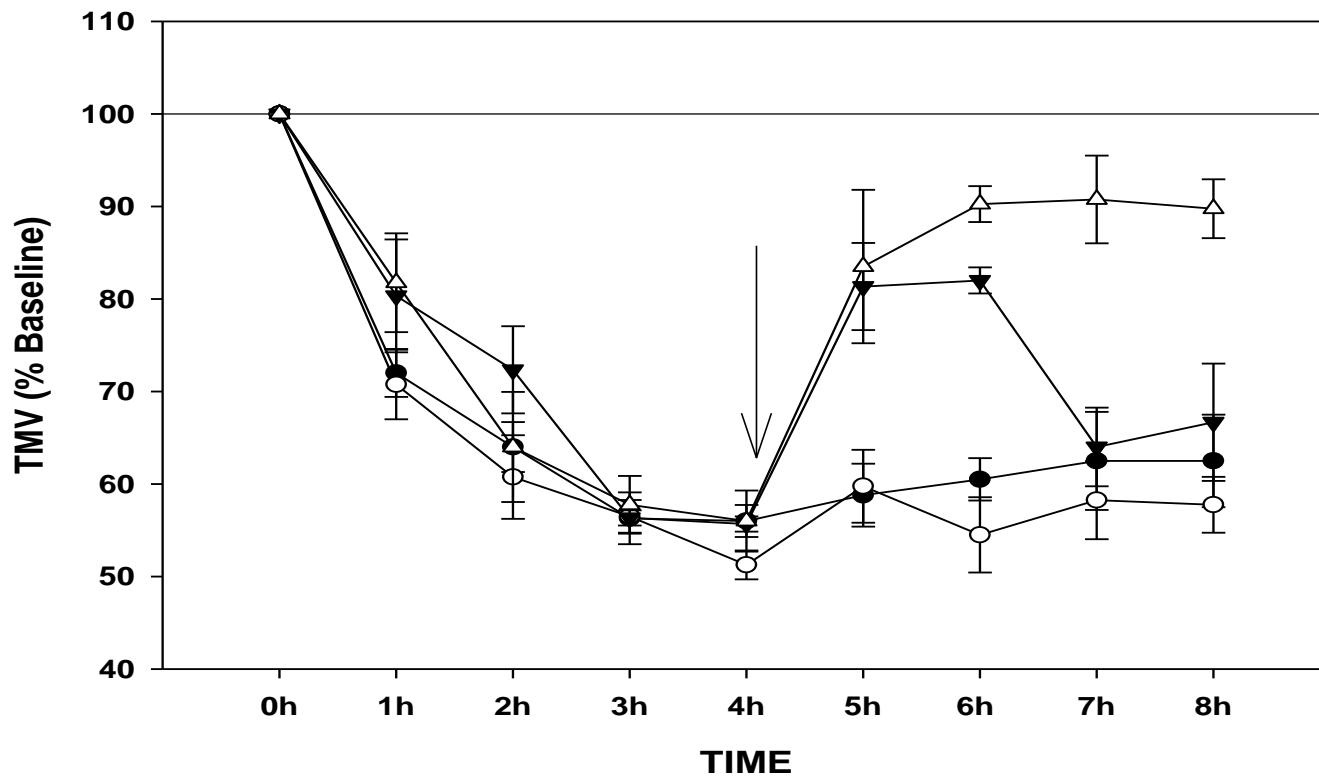
Agent	RL	TMV	Total Cells	Neutrophils
HNE Control	119%	52%	2.8	35
brevenal	24%	76%	1.0	2.7
HS	126%	53%	1.6	9.6
budesonide	77%	56%	1.4	5.1
amiloride	76%	73%	4.2	57.5

- MEAN PULMONARY FLOW RESISTANCE (RL)
- TRACHEAL MUCUS VELOCITY (TMV)
- BRONCHOALVEOLAR LAVAGE (BAL) CELL RESPONSES IN CONSCIOUS SHEEP AFTER AEROSOL CHALLENGE WITH HNE
- AEROSOLS OF HYPERTONIC SALINE (HS, 3ML 7%)
- GLUCOCORTICOSTEROID BUDESONIDE (1MG/3 ML, B.I.D FOR 4 DAYS)
- AMILOLIDE (3ML, 3MM)
- BREVENAL (100 BREATHS OF 50UG/ML),

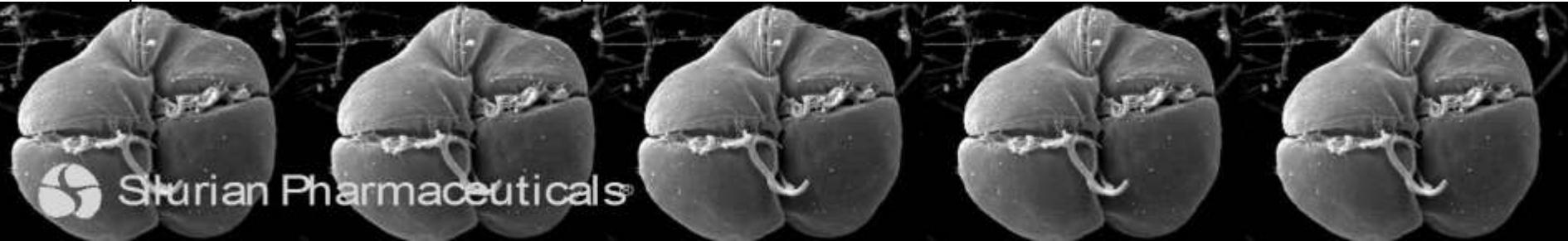


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Effect of Various Treatments on CFTR (inh) -172 Slowing of Tracheal Mucus Velocity



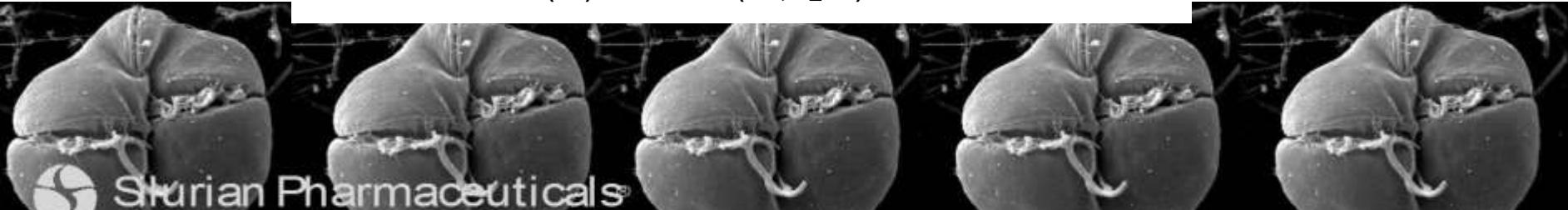
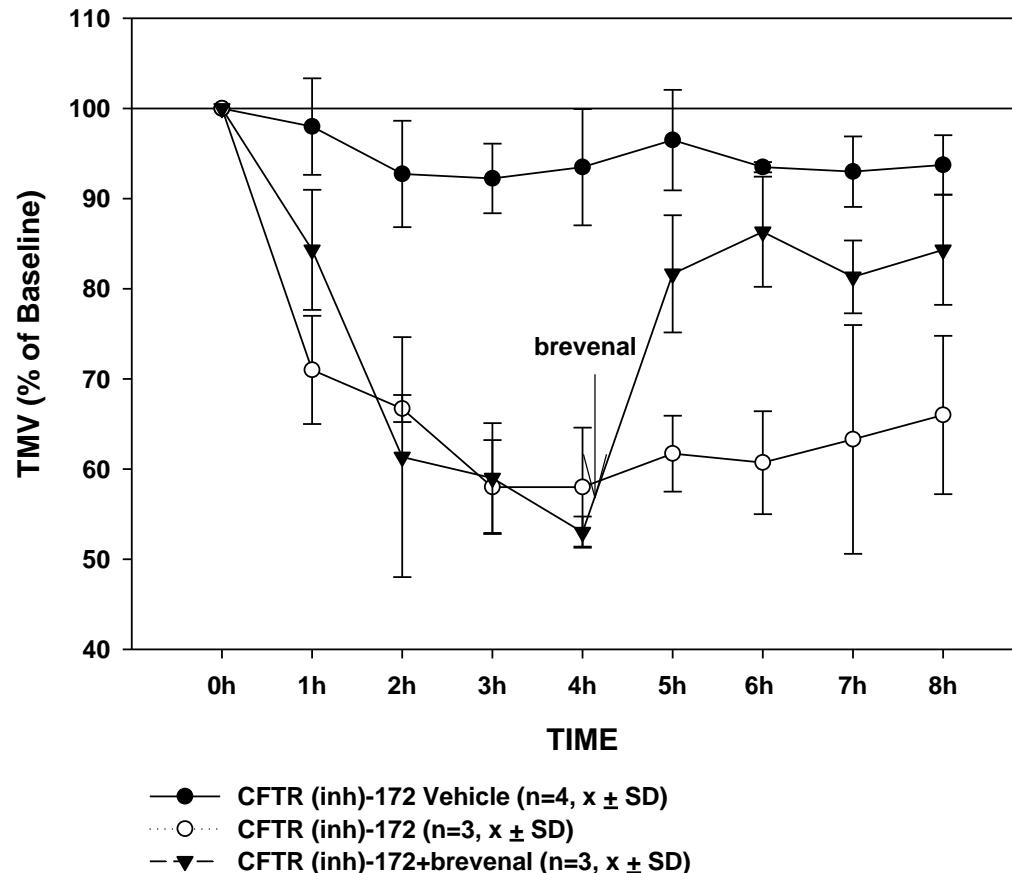
- CFTR(inh)-172
- CFTR(inh)-172 + SNa
- ▼ CFTR(inh)-172 + HS
- △ CFTR(inh)-172 + Amiloride



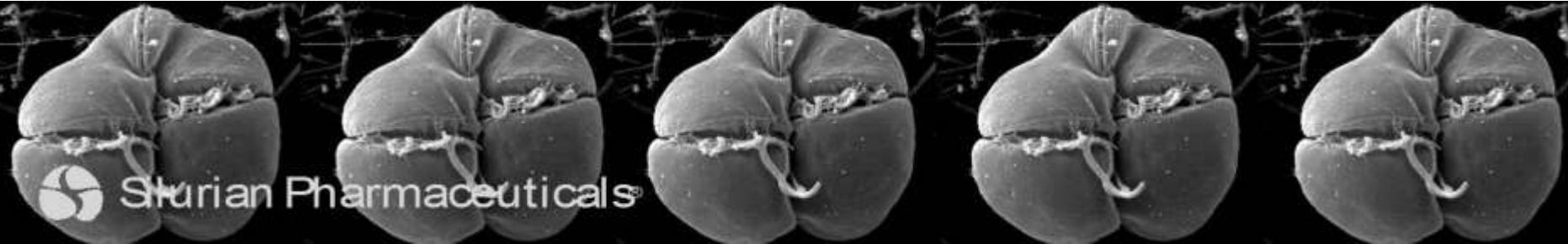
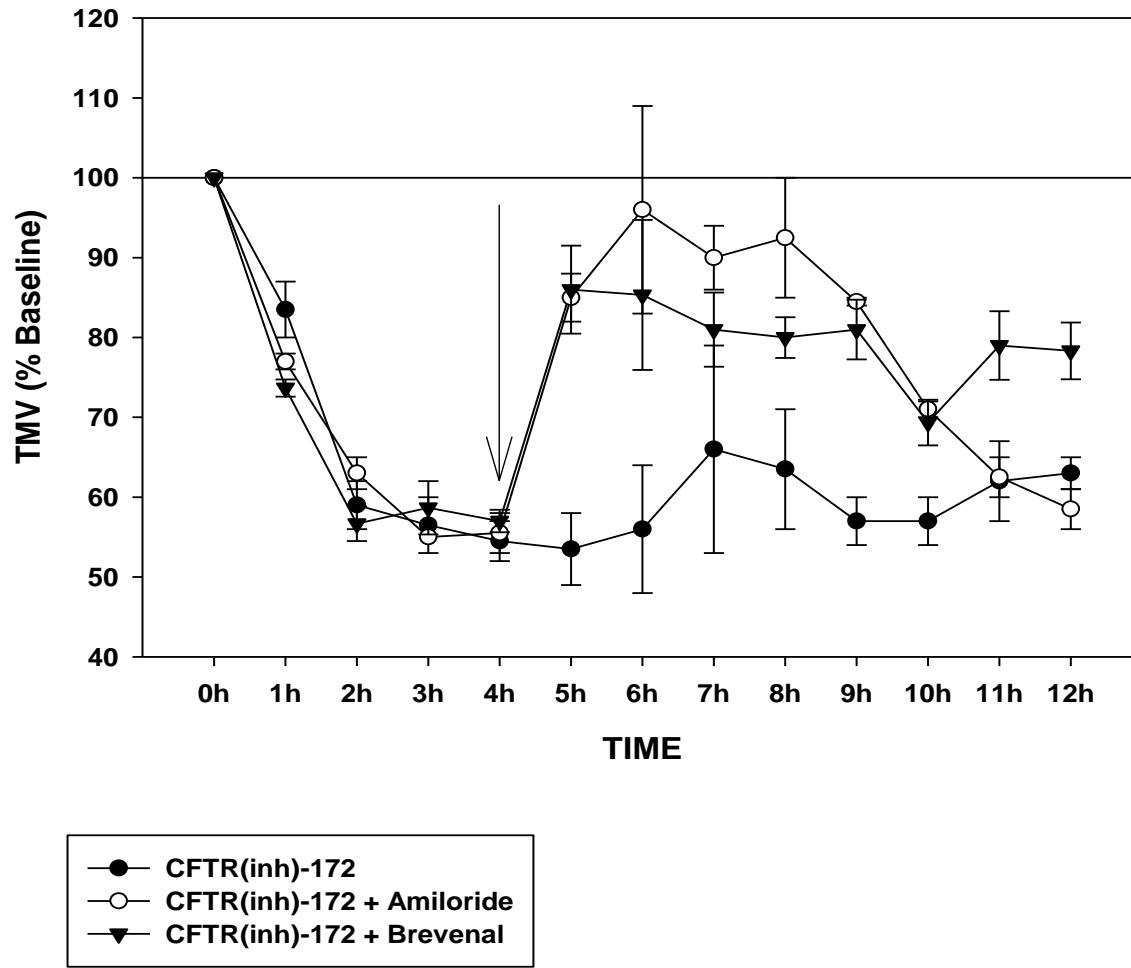
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BREVENAL REVERSES EFFECT OF CFTR INHIBITOR 172 *IN VIVO*

Effect of Brevenal on CFTR inh Induced Reduction in Tracheal Mucus Velocity

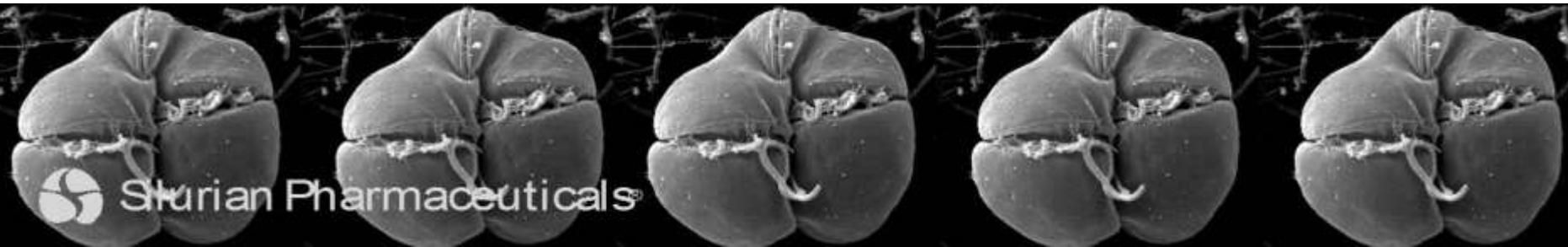
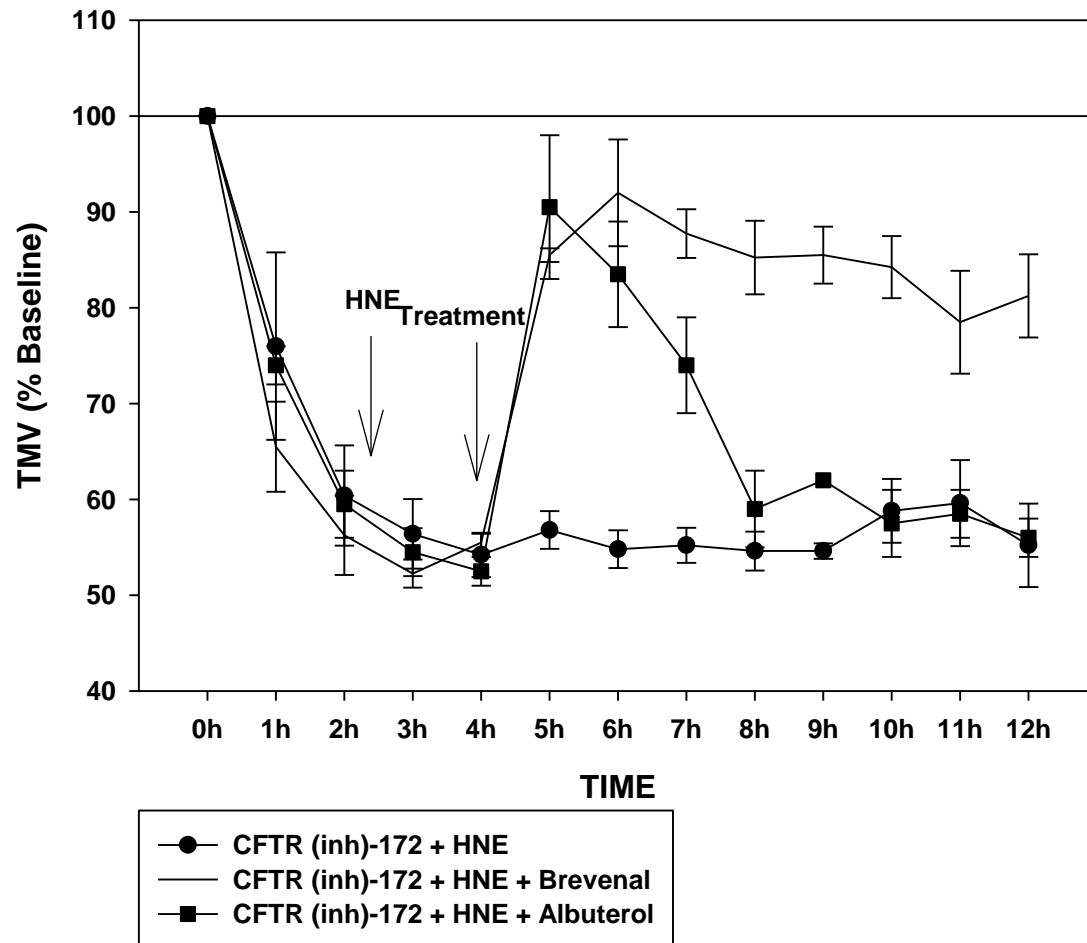


Comparative Time Course Effects of Brevenal and Amiloride on CFTR(inh)-172 Induced Slowing of Tracheal Mucus Velocity



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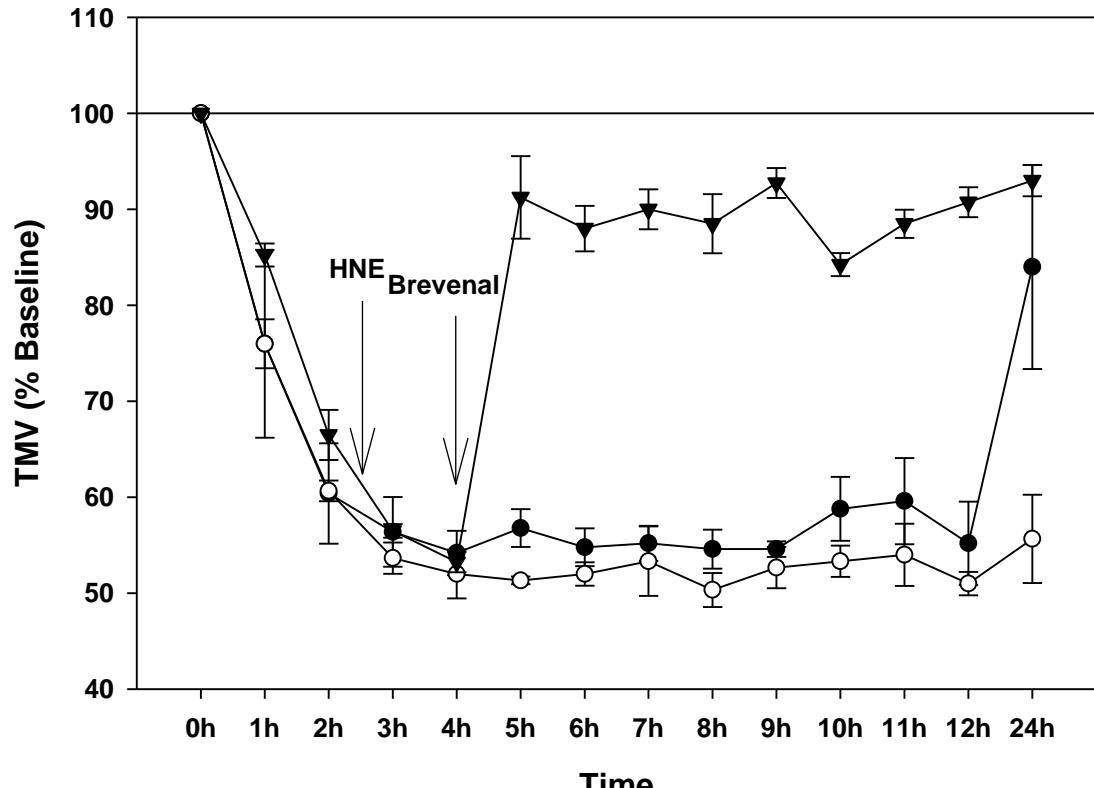
Effect of CFTR (inh) -172 and HNE on Tracheal Mucus Velocity



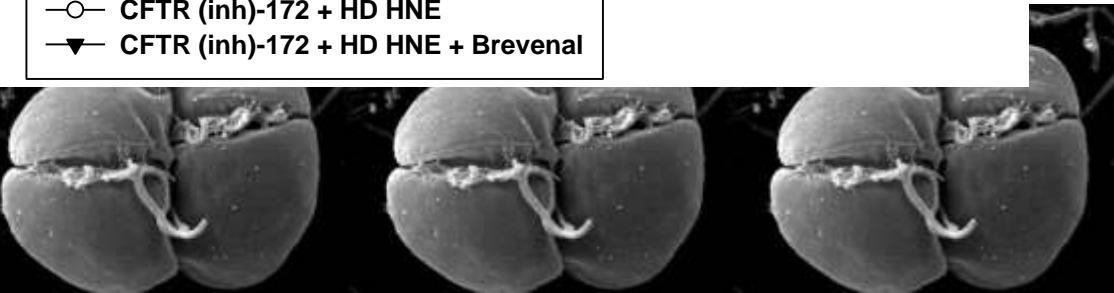
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Brevenal Reverses CFTR (inh)-172 + High Dose HNE-Induced Reduction in TMV

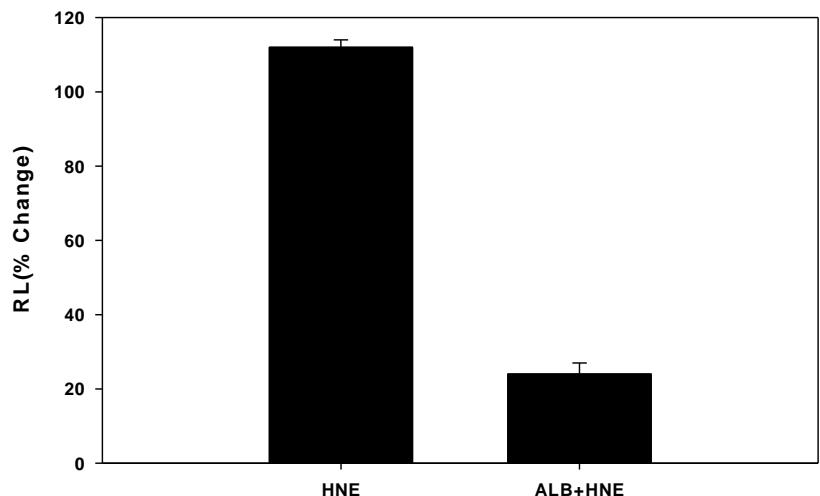
Single dose of Brevenal is effective for 24 hrs following inhibition of MCC by CFTR(inh) 172 plus high dose of HNE



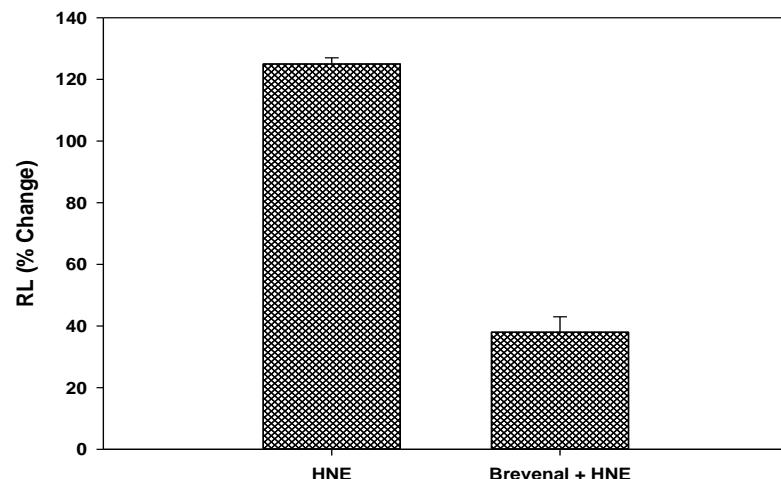
- CFTR (inh)-172 + LD HNE
- CFTR (inh)-172 + HD HNE
- ▼ CFTR (inh)-172 + HD HNE + Brevenal



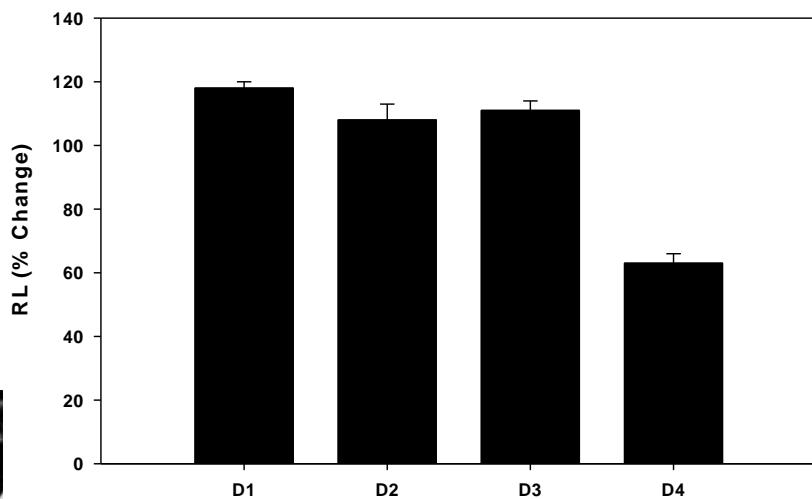
Effect of Albuterol on HNE - Induced Bronchoconstriction



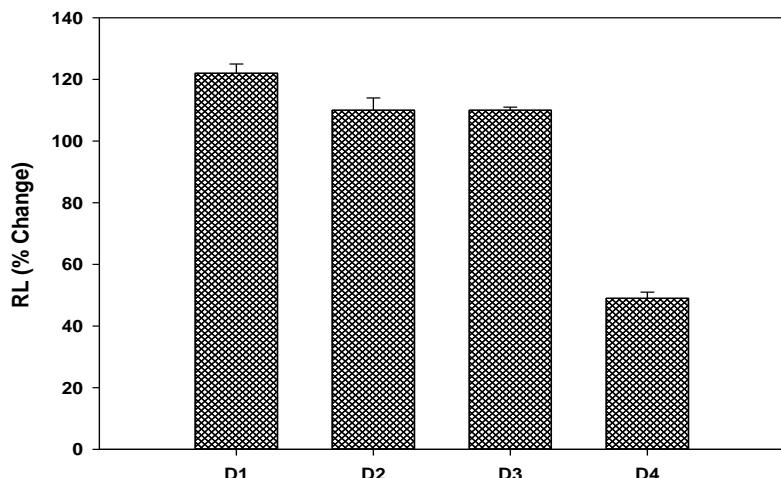
Effect of Brevenal on HNE - Induced Bronchoconstriction



Effect of Albuterol on CFTR(inh) + HNE - Induced Bronchoconstriction

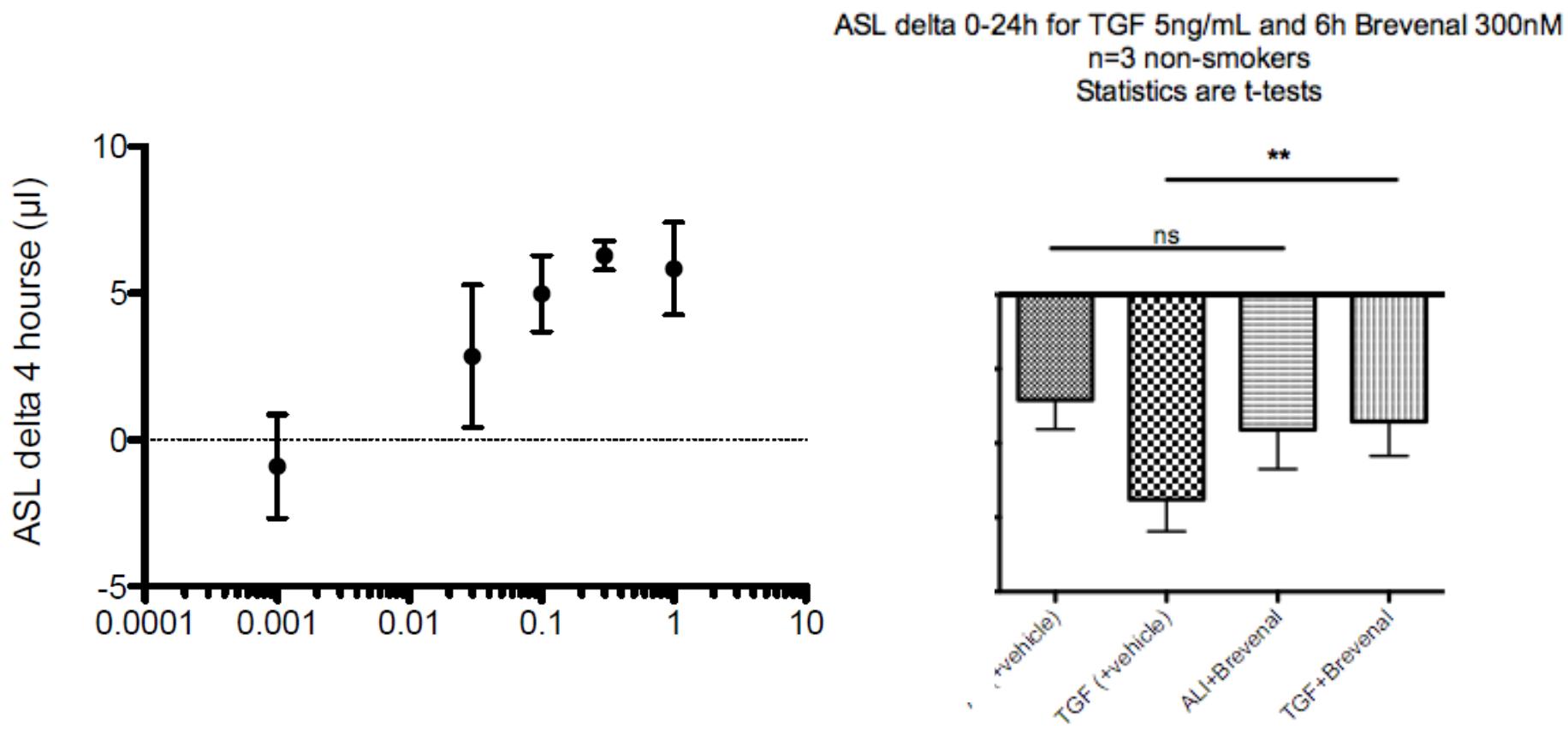


Effect of Brevenal on CFTR(inh) + HNE - Induced Bronchoconstriction



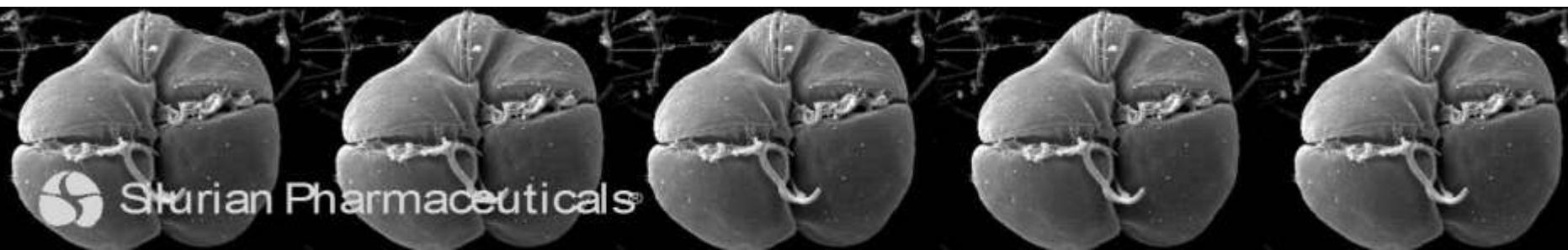
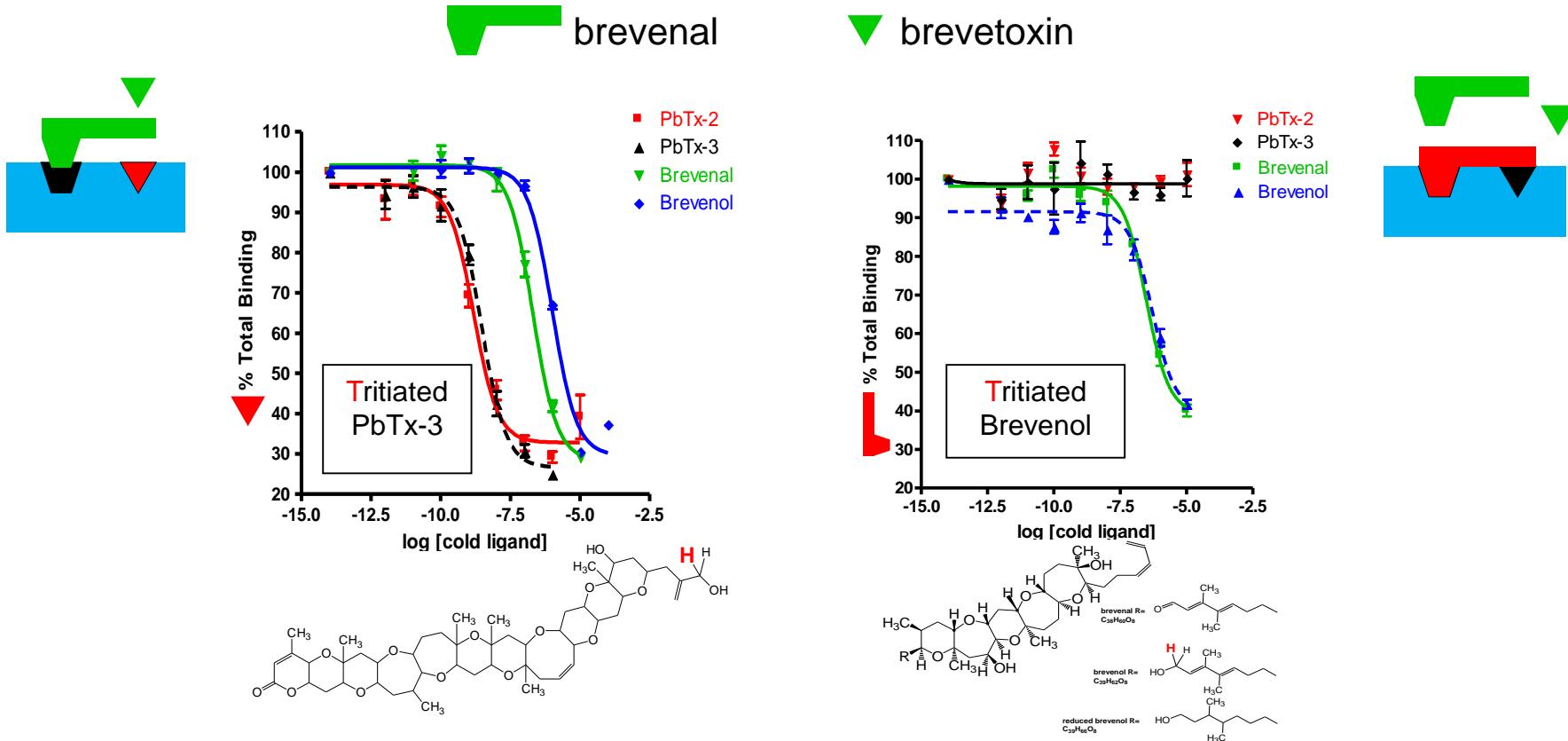
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BREVENAL DOSE RESPONSE ON ASL- DONOR PRIMA



BREVENAL A VOLTAGE SENSITIVE SODIUM CHANNEL INHIBITOR

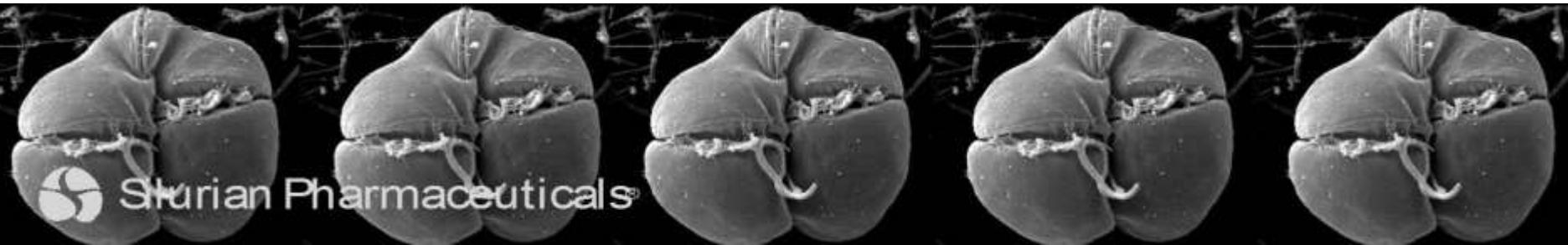
BREVENAL VSSC INHIBITOR, BINDING TO SITE 5 OF VSSC



SUMMARY

EFFECTIVENESS

- BREVENAL IS SUPERIOR TO HS, BUDESONIDE, AMILORIDE, SILVELESTAT SODIUM (AN ELASTASE INHIBITOR) AND ALBUTEROL
- HNE INDUCED CHANGES IN TMV
- HNE INDUCED BC
- HNE INDUCED INFLAMMATION
- SUPERIOR DURATION OF ACTION
- BREVENAL REVERSES MCC INHIBITION CAUSED BY THE CFTRINH 172
- BREVENAL REVERSES MCC INHIBITION CAUSED BY SINGLE AND/OR MULTIPLE CHALLENGES WITH CFTRINH 172 + HNE
- BREVENAL INCREASES ASL IN PRIMARY DONOR CELLS
- BREVENAL BLOCKS TGF β INDUCED ASL ABSORBTION



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