KOPRE CAD/DM & Stent Study

(KOrea PREgrel multicenter Clinical Study for patients with CAD/DM & Stent Implantation)

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Department of Internal Medicine,
Seoul National University Hospital
Contents

- Introduction of Pregrel® (Clopidogrel Resinate)
- KOPRE CAD/DM Study
- KOPRE Stent Study
Clopidogrel is unstable!!

Viscous semi-solid form
Solubility: < 5 ug/mL
Stability: unstable

Clopidogrel (S-enantiomer)

Impurity A
Hydrolysis metabolite

Impurity C
Racemic form
(S + R-enantiomer)

Unknown Impurities
Degradation of Clopidogrel

Initial, 40°C → 3 days, 40°C → 7 days, 40°C
Salt Screening

Acetate  
Aspartate  
Citrate  
Edatate  
Glutamate  
Glycolate  
Glucuronate  
Malate  
Propionate  
Phosphate  
Metaphosphate  
Polyphosphate  
Metabisulfate  
Hydrochlorate  
Tartrate  

Sulfate (Bisulfate) – Sanofi  
Besylate – Helm, Cadila

Clopidogrel does not easily form stable and solid salts with conventional acids, FDA approved acids for salts. It has been stabilized and solidified with sulfate or sulfonate group.
New Polymeric Salt form of Clopidogrel

Drug load: about 50% (48~53%)

Stability: stable

Chemical structure of clopidogrel resinate
## Preliminary Stability

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel-free Base</th>
<th>Clopidogrel-resin Physical mixture</th>
<th>Clopidogrel Resinate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appearance</strong></td>
<td>(A-1)</td>
<td>(B-1)</td>
<td>(C-1)</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>98.63%</td>
<td>95.43%</td>
<td>99.18%</td>
</tr>
<tr>
<td><strong>Total Impurities</strong></td>
<td>0.39%</td>
<td>0.87%</td>
<td>0.28%</td>
</tr>
</tbody>
</table>

| Appearance             | (A-2)                 | (B-2)                             | (C-2)              |
| **Assay**              | 92.21%                | 92.32%                            | 99.61%             |
| **Total Impurities**   | 5.87%                 | 3.66%                             | 0.29%              |

**Appearance**
- 40°C, 75% relative humidity
- 1 week

**Clopidogrel-free Base**
- Appearance: (A-1)
- Assay: 98.63%
- Total Impurities: 0.39%

**Clopidogrel-resin Physical mixture**
- Appearance: (B-1)
- Assay: 95.43%
- Total Impurities: 0.87%

**Clopidogrel Resinate**
- Appearance: (C-1)
- Assay: 99.18%
- Total Impurities: 0.28%
Physical Stability

Clopidogrel resinate (Pregrel ®)  
Clopidogrel bisulfate (Plavix ®)

2 weeks, open condition  
2 weeks, open condition

## Chemical Stability

<table>
<thead>
<tr>
<th>Product</th>
<th>Assay (%)</th>
<th>Hydrolysis product (%)</th>
<th>R-enantiomer (%)</th>
<th>Total impurities (%)</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
<td>3 months(^b)</td>
<td>Initial</td>
<td>3 months</td>
</tr>
<tr>
<td>Pregrel(^®)</td>
<td>102.5</td>
<td>0.07</td>
<td>0.19</td>
<td>0.27</td>
<td>0.32</td>
</tr>
<tr>
<td>Plavix(^®)</td>
<td></td>
<td>97.9</td>
<td>0.04</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Plagil(^®)</td>
<td></td>
<td>95.1</td>
<td>0.45</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Clodrel(^®)</td>
<td></td>
<td>88.7</td>
<td>0.85</td>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>Oravis(^®)</td>
<td></td>
<td>95.6</td>
<td>0.67</td>
<td>1.36</td>
<td></td>
</tr>
<tr>
<td>Nikolot(^®)</td>
<td></td>
<td>91.6</td>
<td>0.86</td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td>Clopigrel(^®)</td>
<td></td>
<td>91.6</td>
<td>0.15</td>
<td>1.40</td>
<td></td>
</tr>
<tr>
<td>Preva(^®)</td>
<td></td>
<td>93.3</td>
<td>0.57</td>
<td>2.54</td>
<td></td>
</tr>
<tr>
<td>Clavix(^®)</td>
<td></td>
<td>93.6</td>
<td>1.46</td>
<td>2.06</td>
<td></td>
</tr>
<tr>
<td>Clopiper(^®)</td>
<td></td>
<td>91.3</td>
<td>&lt;0.01</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Stomix(^®)</td>
<td></td>
<td>86.5</td>
<td>0.07</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Cloplat 75(^®)</td>
<td></td>
<td>95.9</td>
<td>1.36</td>
<td>2.47</td>
<td></td>
</tr>
<tr>
<td>Deplatt(^®)</td>
<td></td>
<td>96.7</td>
<td>0.08</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Ceruvir(^®)</td>
<td></td>
<td>96.1</td>
<td>0.23</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Cloplatic(^®)</td>
<td></td>
<td>90.3</td>
<td>1.47</td>
<td>2.20</td>
<td></td>
</tr>
<tr>
<td>Plagrel(^®)</td>
<td></td>
<td>102.3</td>
<td>0.21</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Nefazan(^®)</td>
<td></td>
<td>96.4</td>
<td>0.07</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Talcom(^®)</td>
<td></td>
<td>94.5</td>
<td>0.04</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Clopifran(^®)</td>
<td></td>
<td>95.3</td>
<td>0.07</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Clopigrel(^®)</td>
<td></td>
<td>97.7</td>
<td>0.17</td>
<td>1.78</td>
<td></td>
</tr>
</tbody>
</table>

\(^b\) Chemical Stability

Selective Permeability in Pregrel

Permeation constant of Clopidogrel and resinate across Caco-2 cell monolayers from apical(A) to basolateral(B) side.

<table>
<thead>
<tr>
<th></th>
<th>( P_{\text{app}} ) of Clopidogrel</th>
<th>( P_{\text{app}} ) of Salts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clopidogrel resinate</strong></td>
<td>( 13.5 \times 10^{-6} ) cm/sec</td>
<td>( 0.0 \times 10^{-6} ) cm/sec</td>
</tr>
<tr>
<td><strong>Clopidogrel bisulfate</strong></td>
<td>( 12.7 \times 10^{-6} ) cm/sec</td>
<td>( 26.6 \times 10^{-6} ) cm/sec</td>
</tr>
<tr>
<td><strong>Clopidogrel besylate</strong></td>
<td>( 11.9 \times 10^{-6} ) cm/sec</td>
<td>( 8.0 \times 10^{-6} ) cm/sec</td>
</tr>
<tr>
<td><strong>Clopidogrel napadisylate</strong></td>
<td>( 14.9 \times 10^{-6} ) cm/sec</td>
<td>( 7.8 \times 10^{-6} ) cm/sec</td>
</tr>
</tbody>
</table>

* The correlation between the permeability coefficient \( (P_{\text{app}}) \) across Caco-2 cell monolayer and the oral bioavailability \( (F) \) in the intestinal tract.

<table>
<thead>
<tr>
<th>( P_{\text{app}} ) (permeability coefficient, cm/sec)</th>
<th>( F ) (oral bioavailability, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( &lt; 1.0 \times 10^{-6} )</td>
<td>( &lt; 10% )</td>
</tr>
<tr>
<td>( 1.0 \times 10^{-6} - 10.0 \times 10^{-6} )</td>
<td>( 10% - 90% )</td>
</tr>
<tr>
<td>( &gt; 10.0 \times 10^{-6} )</td>
<td>( &gt; 90% )</td>
</tr>
</tbody>
</table>
Resinate is not absorbed from the gastrointestinal (GI) tract, and carries the active drug (clopidogrel) into the body.
Toxicity in animal experiment

Safety Study of Clopidogrel Resinate

A. Single-dose study
B. Dose range-finding study (4 weeks)
C. Multiple-dose study (13 weeks)
D. Toxicokinetics in multiple-dosing (13 weeks)
E. Mutagenicity

Comparative toxicity: oral lethal dose, 50%

<table>
<thead>
<tr>
<th>API *</th>
<th>LD$_{50}$ ** (Rat) Male</th>
<th>LD$_{50}$ ** (Rat) Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel Resinate</td>
<td>&gt; 2,000 mg/kg</td>
<td>&gt; 2,000 mg/kg</td>
</tr>
<tr>
<td>Clopidogrel Bisulfate</td>
<td>1,800 mg/kg</td>
<td>2,000 mg/kg</td>
</tr>
</tbody>
</table>

[Reference] GLP toxicity study report of Clopidogrel resinate

* API: Active Pharmaceutical Ingredient

**LD$_{50}$: The amount of a chemical that is lethal to one-half (50%) of the experimental animals orally exposed to it
Phase I: Pharmacokinetics profiles

Healthy volunteers

Center: Asan medical center
Subject: 48, cross-over

PK profiles of Clopidogrel (Parent drug)

PK profiles of 1st Clopidogrel Metabolite
Phase I: Pharmacodynamics profiles
Healthy volunteers

300mg → 75mg qd for 7 days

center: Asan medical center
subject: 48, cross-over

- Pregrel (CKD)
- Plavix (Sanofi)
KOPRE-CAD/DM Study in 10 Centers
Background

- Clopidogrel generic drugs
  - PK/PD studies: healthy volunteers
  - Not evaluated in the real-world CAD or DM patients in Korea

- Aim of this study
  - To validate the ADP blocking activity of clopidogrel resinate (Pregrel®) in the real-world pts
  - To compare the antiplatelet activity of clopidogrel resinate (Pregrel®) with clopidogrel bisulfate (Plavix®)
Study Design

- Double-blind, randomized, prospective multicenter trial
- Coronary Artery Disease (CAD) or CAD equivalent patient
- Treatment
  - Pregrel+Aspirin vs. Plavix+Aspirin vs. Placebo+Aspirin
  - 4 weeks
- Primary endpoint
  - VerifyNow™ P2Y12 assay % inhibition
- Secondary endpoint
  - Safety profile, hs-CRP, lipid profile change in atorvastatin users
## Participating 10 Centers in Korea

<table>
<thead>
<tr>
<th>Site</th>
<th>Principle Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajou University Medical center</td>
<td>Tahk, Seung Jea</td>
</tr>
<tr>
<td>Seoul ST. Mary’s Hospital</td>
<td>Seung, Kie Bae</td>
</tr>
<tr>
<td>Gyeongsang Natinal University Hospital</td>
<td>Kwak, Chung Hwan</td>
</tr>
<tr>
<td>Kyung Hee University Medical Center</td>
<td>Kim, kwon Sam</td>
</tr>
<tr>
<td>Korea University Anam Hospital</td>
<td>Hong, Soon Jun</td>
</tr>
<tr>
<td>Dong-A Medical center</td>
<td>Park, Tae Ho</td>
</tr>
<tr>
<td>Boramae Hospital</td>
<td>Kim, Sang Hyun</td>
</tr>
<tr>
<td>Seoul National University Hospital</td>
<td>Kim, Hyo Soo</td>
</tr>
<tr>
<td>Cheju National University Hospital</td>
<td>Joo, seung Jae</td>
</tr>
<tr>
<td>Hallym University Medical Center</td>
<td>Choi, young Jin</td>
</tr>
</tbody>
</table>
Inclusion Criteria

- Coronary Artery Disease or CAD equivalent patients
  - Coronary Artery Disease
    - Detected any Atherosclerotic plaque by Coronary CT or Angiography
    - Positive stress test
    - History of PCI or CABG (>1yr)
  - Diabetes Mellitus
  - Carotid atherosclerotic plaque
  - Peripheral Artery disease including cerebrovascular disease

- Age: 20~85yrs
- Able to give informed consent
Exclusion Criteria

- History of PCI within 1 year of entry into the study
- Concomitant use of antiplatelet agents such as clopidogrel, cilostazol
  - **Washout period**
- Concomitant use of anticoagulants
- Chronic alcoholism
- Hypersensitivity to aspirin or clopidogrel
- History of gastrointestinal bleeding or intracranial hemorrhage bleeding
- Blood coagulation disorders, uncontrolled severe hypertension
- History of severe bleeding, active bleeding
- Pregnancy or breast feeding
Flow Chart of KoPre-CAD/DM trial

**Screening period**
- Visit 1: Baseline number, Screening
- Day -28~ -1

**Double-Blind treatment period**
- Visit 2: Day 0, Randomization, Allocation number, Verifinow P2Y12, Lab test, Angina Class
- Visit 3: Day 27 ± 5, Investigational drugs return, Verifinow P2Y12, Lab test, Angina class, Adverse Event

**Wash-out**
- Investigational drugs once daily
Hypothesis & allocation of patients

- Pregrel+aspirin / Plavix+aspirin superior to aspirin in the inhibition of ADP receptor
- Pregrel+aspirin non-inferior to Plavix+aspirin

- N= 330 pts (including 10% drop out)
- Stratification by DM (40% for each group)
- Statin : atorvastatin exclusively
Results
Patient distribution

Screened (n=321)

Randomized (n=314)

Placebo + Aspirin (n=105)
- n=2
- n=103
  - Discontinued (n=6)
    - Adverse event 0
    - Protocol violation 6
    - Voluntary withdrawal 0
  - Completed study (n=97)

Pregrel + Aspirin (n=103)
- n=3
- n=100
  - Discontinued (n=10)
    - Adverse event 3
    - Protocol violation 6
    - Voluntary withdrawal 1
  - Completed study (n=90)

Plavix + Aspirin (N=106)
- n=3
- n=103
  - Discontinued (n=3)
    - Adverse event 0
    - Protocol violation 3
    - Voluntary withdrawal 0
  - Completed study (n=100)

Discontinued (n=6)
- Protocol violation 6
- Voluntary withdrawal 0

Completed study (n=97)

Completed study (n=90)

Completed study (n=100)
## Baseline Characteristics of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Aspirin (n=103)</th>
<th>Pregrel + Aspirin (n=100)</th>
<th>Plavix + Aspirin (n=103)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age y, Mean (SD)</td>
<td>62.1 ± 9.7</td>
<td>62.1 ± 8.1</td>
<td>62.7 ± 8.9</td>
<td>0.82</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>65 (63.1)</td>
<td>68 (68.0)</td>
<td>62 (60.2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>41 (39.8)</td>
<td>40 (40.0)</td>
<td>41 (39.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>87 (84.5)</td>
<td>91 (91.0)</td>
<td>85 (82.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>37 (35.9)</td>
<td>29 (29.0)</td>
<td>40 (38.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>History of CHD, n (%)</td>
<td>88 (85.4)</td>
<td>73 (73.0)</td>
<td>91 (88.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of PCI</td>
<td>40 (38.8)</td>
<td>37 (37.0)</td>
<td>47 (45.6)</td>
<td>0.42</td>
</tr>
<tr>
<td>History of carotid artery disease, n (%)</td>
<td>5 (4.9)</td>
<td>4 (4.0)</td>
<td>3 (2.9)</td>
<td>0.82</td>
</tr>
<tr>
<td>History of peripheral artery disease, n (%)</td>
<td>7 (6.8)</td>
<td>5 (5.0)</td>
<td>6 (5.8)</td>
<td>0.86</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>19 (18.5)</td>
<td>23 (23.0)</td>
<td>16 (15.5)</td>
<td>0.41</td>
</tr>
</tbody>
</table>
P2Y$_{12}$ receptor inhibition among three groups:

- **All Patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>% P2Y$_{12}$ Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (n=96)</td>
<td>-5.9</td>
</tr>
<tr>
<td>Pregrel+aspirin (n=100)</td>
<td>23.4</td>
</tr>
<tr>
<td>Plavix+aspirin (n=96)</td>
<td>19.5</td>
</tr>
</tbody>
</table>

- $p < 0.001$ for non-inferiority
- $p = 0.17$
- $p = 0.02$
Subgroup analysis: CHD patients

% P2Y12 inhibition

Aspirin (n=83)
-6.5

Pregrel+aspirin (n=73)
22.5

Plavix+aspirin (n=85)
20.6

Statistical significance:
- $p < 0.001$
- $p = 0.64$
Subgroup analysis: DM patients

Aspirin (n=39)  Pregrel+aspirin (n=37)  Plavix+aspirin (n=38)

-4.3  23.1  16.9

% P2Y12 inhibition

p < 0.001

p = 0.64

p < 0.001
Subgroup analysis: Atorvastatin Users

- Aspirin (n=41): -5.1, p <0.001
- Pregrel+aspirin (n=47): 22.6, p =0.42
- Plavix+aspirin (n=44): 18.9, p <0.001

% P2Y12 inhibition

KoPre-Study
Non-inferiority comparison of Pregrel & Plavix: by the difference of %P2Y12 inhibition

Non-inferiority margin – 5.7

All patients

CHD

DM

Atorvastatin users

Difference of
P2Y12 inhibition %

Pregrel (Clopidogrel Resinate) Inferior

Pregrel (Clopidogrel Resinate) non-inferior
## Adverse Events during the study

<table>
<thead>
<tr>
<th>Category</th>
<th>Aspirin (n=103)</th>
<th>Pregrel+Aspirin (n=100)</th>
<th>Plavix+aspirin (n=103)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>34 (33.0)</td>
<td>26 (26.0)</td>
<td>24 (23.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 (0.97)</td>
<td>3 (3.0)</td>
<td>1 (1.0)</td>
<td>0.42</td>
</tr>
<tr>
<td>Serious drug-related AEs</td>
<td>0</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0.36</td>
</tr>
</tbody>
</table>
KOPRE-CAD/DM Conclusion

- Clopidogrel resinate in CHD/CHD equivalents
  - Non-inferior antiplatelet effect to original form of clopidogrel bisulfate
  - Similar safety profile to negative control

- Safe substitute for clopidogrel bisulfate in atherosclerotic vascular disease
KOPRE-Stent Study in 4 Centers
Background

- Pharmacokinetics & Pharmacodynamics Study
  - Healthy volunteers

- KOPRE CAD/DM Study
  - Clopidogrel resinate can be substituted for Clopidogrel bisulfate and prescribed safely in stable OPD patients with CAD/DM

- KOPRE Stent Study
  - To validate the efficacy of Pregrel in CAD patients undergoing stent implantation
Aim of this study

- To validate the ADP blocking activity of Clopidogrel Resinate (Pregrel®) in patients with stent implantation

- To evaluate the death, MACE, safety of Pregrel® group comparing with Plavix® group for 4 weeks
Study Design

- A randomized, open-label, comparative, parallel group

- Treatment
  - Pregrel + Aspirin vs Plavix + Aspirin

- Primary endpoint
  - VerifyNow™ P2Y12 assay % inhibition

- Secondary endpoint
  - MACE, Safety Profile, Cardiac Enzyme
Inclusion Criteria

- Coronary Artery Disease patients requiring Stent Implantation

- Age: 20~85yrs

- Able to give informed consent
Coronary Artery Disease pts. Requiring Stent implantation

* Pregrel or Plavix Loading dose 300mg Prior to Stent (1day) (Before 6 hours: 600mg)

- Pregrel 75mg + Aspirin
- Plavix 75mg + Aspirin

-1day  Day 0  Day 28 ± 7

Enrollment & Randomization  Verifinow P2Y12 & Cardiac enzyme  Verifinow P2Y12
Participating 4 Centers in Korea

<table>
<thead>
<tr>
<th>Site</th>
<th>Principle Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyung Hee Hospital at Kangdong</td>
<td>Kim, Chong Jin</td>
</tr>
<tr>
<td>Konyang University Hospital</td>
<td>Bae Jang Ho</td>
</tr>
<tr>
<td>Daegu Catholic Uni. Medical Center</td>
<td>Kim, Kee Sik</td>
</tr>
<tr>
<td>Seoul National University Hospital</td>
<td>Kim, Hyo Soo</td>
</tr>
</tbody>
</table>
Results
VerifyNow P2Y12 % inhibition

1day

- 프리그렐: 27.43 (n=53)
- 플라빅스: 27.02 (n=58)

1month

- 프리그렐: 24.29 (n=51)
- 플라빅스: 30.84 (n=56)

P=0.92

P=0.1
VerifyNow PRU

- 1 day:
  - 프리그렐: 241.58 (n=53)
  - 플라빅스: 241.98 (n=58)
  - P = 0.98

- 1 month:
  - 프리그렐: 239.49 (n=51)
  - 플라빅스: 218.14 (n=56)
  - P = 0.17
<table>
<thead>
<tr>
<th>Category</th>
<th>Pregel (n=54)</th>
<th>Plavix (n=59)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>16 (29.6)</td>
<td>18 (30.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>0 (0.0)</td>
<td>2 (3.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Drug-related AEs</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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</tr>
</tbody>
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Conclusion

- Clopidogrel resinate in patients with PCI
  - No difference in efficacy & safety between Pregrel® and Plavix®

- Safe substitute for clopidogrel bisulfate in CAD patients undergoing stent implantation
## Comparison of Price

<table>
<thead>
<tr>
<th></th>
<th>Price (₩)</th>
<th>Daily cost</th>
<th>Monthly cost</th>
<th>Yearly cost</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Plavix</td>
<td>2,014</td>
<td>2,014</td>
<td>60,420</td>
<td>735,110</td>
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<tr>
<td>Generic A</td>
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<td>1,733</td>
<td>51,990</td>
<td>632,545</td>
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<tr>
<td>Pregrel</td>
<td>919</td>
<td>919</td>
<td>27,570</td>
<td>335,435</td>
<td>100</td>
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</tbody>
</table>
All that glitters is NOT gold........