Aligen Therapeutics SL

New antihemorrhagic agents: a novel antifibrinolytic strategy

- **Hemorrhage** is a leading cause of death and cost associated with blood transfusion.
- There is a **need** for the improvement of current treatments of bleeding associated with **surgery**, **trauma**, **intracerebral hemorrhage** (ICH) or other tissue damages.
- A **novel target** involved in fibrinolysis has been identified.
- **Proprietary novel compounds** to prevent major bleeding have been developed:
  - Small molecule entity (SME).
  - Efficacy: 30,000 times more effective than the currently available therapies.
  - Safety: No thrombus formation and no impact on coagulation.
- **Primary Indication: prophylaxis and acute treatment of bleeding in cardiac surgery.**
- **Life plan** intravenous: cardiac surgery → other major surgeries → trauma and first-aid → ICH
  topical: trauma and first-aid → OTC → veterinary uses

Scope of the problem

- Coronary arteries bypass surgery: 470,000 procedures/year in the 7 Major Markets. Aprotinin withdrawal ($600M market niche) has generated demand and opportunity for new antifibrinolytics that could significantly reduce the number of blood transfusions.
- **Major surgeries**: 100-120 million procedures every year in the 7 Major Markets, 2.5-3.5% with significant blood loss. Tranexamic acid (TXA) is used in 35-45% of surgeries.
- Annual expenditures on blood transfusion: $1.62M-$6.03M per hospital.
- Hemorrhage is responsible for 50% deaths occurring within 24 h of **traumatic injury**.
- **Intracerebral hemorrhage** (ICH; 15% of all strokes), is associated with high mortality (40%) and there is **no proven medical** or surgical **treatment**.

Patient needs addressed

Prophylaxis and treatment of major bleeding in patients undergoing cardiac surgery
Major bleeding (Guidelines ISTH) in trauma and other clinical and surgical settings.

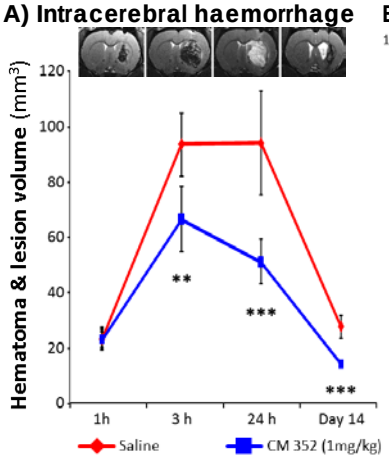
Current Standard of Care & Competitive Landscape

- Antifibrinolytics are the Standard of Care for hemorrhage in surgery and trauma.
- TXA is the only commercially available agent, partially effective at high doses with significant side-effects. Current products in development are restricted to sealants (topical) and clotting factors (plasma derived compounds with higher risk of viral transmissions and thromboembolic complications).

Product Profile

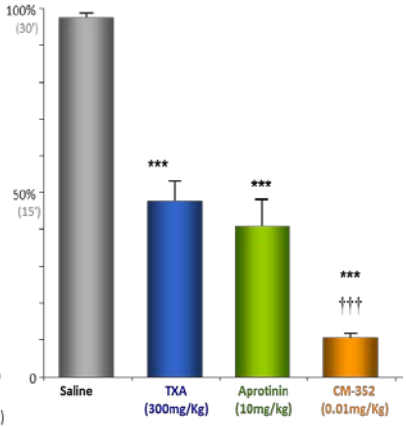
- A new mechanism of action that impacts on fibrinolytic function and not on haemostasis and coagulation.
- Multifactorial process led to optimized compound **CM-352**, safe and efficacious in 4 different *in-vivo* models:
  - i.- Intracerebral hemorrhage (ICH) after early (1h, *Figure A)* and late (3h) administration
  - ii.- Tail bleeding associated with tPA. *Figure B*
  - iii.- Hepatectomy *(severe bleeding) blood lost reduced by CM-352 (p<0.05)but not by TXA.*
  - iv.- Anticoagulant (3 mg/kg Rivaroxaban) associated tail bleeding (p<0.001).
- **CM-352:** Optimal profile for acute systemic administration (i.v.) with short half-life, ideal for short term control of bleeding.

A) Intracerebral haemorrhage



Collagenase-induced ICH
Mean±SME; n=6 rats/group;
** p<0.01; *** p<0.001 vs saline

B) Tail bleeding model



Mean±SME; n≥10 mice/group
* p< 0.05; *** p<0.001 vs saline
††† p<0.001 *vs* TXA.

Intellectual Property US9440989; EP2877446B; AU2013292076B; Pending in Canada and Japan.

Papers Orbe J et al. *J Med Chem*. 2015;58(7):2941-57. Orbe J et al. *J Med Chem*. 2015;58(5):2465-88. Rodriguez JA. et al. J Am Heart Assoc. 2017 (doi:10.1161/JAHA.117.006042).

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