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Pro Bono Bio announces the successful development of subcutaneous and long-acting blood factors VIIa, VIII and IX for the treatment of haemophilia

Subcutaneous blood factors expected to revolutionise the treatment paradigm of haemophiliac patients worldwide

Pro Bono Bio Group plc ("PBB"), the international healthcare group, announces the successful conclusion of a series of pre-clinical trials in haemophiliac subjects conducted with the world's first long acting blood Factors VIIa, VIII and IX capable of subcutaneous administration. The results of these trials are of great importance as these novel long-acting, subcutaneous blood factors are expected to revolutionise the treatment paradigm for haemophilia sufferers worldwide. The availability of PBB's subcutaneous blood factors would make self-administration by patients at home much easier leading to a significant improvement in treatment compliance and reduction in healthcare system costs by avoiding the need for regular IV infusions.

Key findings from the 8 trials with 6 products conducted at the University of Alabama were:

- PBB's current subcutaneous form of FVIIa achieved up to 3 days of haemostatic cover providing the prospect of sustained prophylactic treatment for haemophilia A patients who suffer an immune response to FVIII meaning that FVIII is no longer a viable therapy for them.

- PBB's current intravenous form of Factor VIIa achieved a 12x extension of haemostasis over current commercially available products. This means it could offer significant advantages in trauma applications in hospitals where haemostatic cover can be maintained for the duration of long operations and post-operation, without the current need for multiple administrations and related complications.

- PBB's subcutaneous form of Factor VIII for haemophilia A achieved a circulating dose level of 20% of the intravenous version and also maintained haemostasis for 72 hours, meaning that it is already suitable for twice-weekly dosing and will be able to be administered at higher subcutaneous doses enabling once weekly dosing or better.

- PBB's subcutaneous form of FIX for haemophilia B maintained haemostasis for 10 days meaning that it is already suitable for dosing less frequently than once per week.

- PBB expects to optimise these products so that each one will provide haemostatic cover for at least a week and possibly two weeks from a single subcutaneous injection (with circulating blood factor maximum dose levels ("Cmax") in line with the Malmo Protocol).

Following these successful trials PBB now has 6 blood factor products under development of which 3 can be administered subcutaneously and 3 by intravenous ("IV") injection. Each of these blood factor products has proven efficacy in a sophisticated combination of *in vivo*trials in naturally haemophiliac subjects and *in vitro* assays. PBB's novel improved blood factors utilise the epitope-cloaking property of PEG to prevent the products from being rapidly detected and destroyed by the patient's own immune system before the product has had a chance to fulfil its therapeutic potential. This property has already been demonstrated by PBB in a haemophilia B dog. Work is underway to demonstrate that PBB's other blood factor products are similarly "immune-silent".

PBB intends to optimise these products, confident that effective prophylactic cover will now be possible with each of these blood factors via a once-a-week regimen of shallow subcutaneous injections.

Professor Ted Tuddenham, emeritus Professor of Haemophilia at University College London and former Director of the Haemophilia Centre at the Royal Free Hospital, a pioneer in the development of gene therapy treatments for haemophilia commented “I consider these products to be a vital breakthrough by PBB as the availability of subcutaneous and long acting blood factors will dramatically improve the quality of life and treatment regimes for haemophilia sufferers. There is a clear and present need for these products, which in the longer term, will continue to augment potential gene therapy options.”

John Mayo, CEO of PBB said, “This is great news. These new, improved blood factors have the potential to revolutionise the quality of life for haemophilia sufferers. These new products also have huge commercial potential. It is medically, morally and commercially important that these products get to market as quickly as possible.”

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Further Information

Overview of PBB’s blood factor technology
PBB has been able to generate these improved blood factors that retain their efficacy and have a longer half-life while being capable of subcutaneous administration by attaching an inert molecule of polyethylene glycol (“PEG”) to each individual blood factor molecule in a precise location remote from the active site on each blood factor. PBB’s technology has been applied and tested successfully on several recombinant and plasma sourced blood factor proteins.

- PBB has enhanced the performance of blood factors by pioneering the PEGylation of these proteins with TheraPEG™ technology, developed independently by Polytherics Ltd.

- The recombinant human protein molecules are conjugated to a polyethyleneglycol (“PEG”) molecule. TheraPEG™ technology is uniquely successful where previous attempts to PEGylate blood factors have failed, by carefully locating PEG remotely from the active site on each protein, and by covering epitopes which otherwise trigger an immune response.

- The careful individual pegylation of each molecule ensures that, molecule by molecule, the blood factors are made more water soluble. This enables subcutaneous delivery and allows the products to be formulated with less polysorbate, reducing the total amount of polyethylene glycol administered to a patient (when compared to conventional prophylaxis).

- PBB has substantial intellectual property around these products, including exclusive global licences to TheraPEG™ in relation to these blood factors, in addition to PBB’s own patents.

Summary observations from PBB’s blood factor trials

Subcutaneous delivery

PBB achieved a world first in correcting the whole-blood clotting times of naturally haemophilic dogs to normal via a low-volume subcutaneous injection. As expected, unmodified proteins that were administered subcutaneously in the same studies (and at equivalent dose levels) were ineffective in providing haemostatic cover.

Blood Factor	Naked protein Haemostatic cover (i)	PBB protein Haemostatic cover (i)	Extension of duration of Haemostasis	Expected PBB Protein Haemostatic Cover	Subcutaneous Bioavailability
FVIIa	0 hrs	72 hrs	--∞	168+ hrs	89%
FVIII	0 hrs	72 hrs	--∞	168+ hrs	40% (ii)
FIX	0 hrs	240 hrs	--∞	336 hrs	86%

(i) The duration of "cover" is the time over which a whole blood clotting time of less than 12 minutes could be maintained

(ii) FVIII bioavailability figure reflects a minimum measurement (based on assays for the existing native protein) that is expected to improve as PBB develops specific assays for the new, improved protein.

Further extensions in duration of cover with the subcutaneous products are confidently expected since the Cmax of the subcutaneous products is significantly lower than for the intravenous products, providing plenty of scope for safe dose increases and further product optimisation.

Intravenous delivery

Long-acting intravenous products are ideal for trauma applications including surgical and post-surgical treatment. PBB's modified blood factors clearly outperformed the currently available products (naked protein) in all trials.

Blood Factor	Naked protein Haemostatic cover (i)	Current PBB protein Haemostatic cover (i)	Extension of duration of Haemostasis	Expected PBB Protein Haemostatic Cover
FVIIa	8 hrs	96hrs	12x	168 hrs
FVIII	24 hrs	96 hrs	4x	168 hrs
FIX	72 hrs	240 hrs	3x	336 hrs

(i) The duration of "cover" is the time over which a whole blood clotting time of less than 12 minutes could be maintained

PBB is confident that with regular product optimisation normal haemostatic cover of at least one week will be achieved for all 3 blood factors, both intravenously and subcutaneously.

These improved blood factors make possible, for the first-time, a subcutaneous, long-acting prophylactic regime that would lead to substantial improvements to the quality of life for haemophiliacs. Ease of administration, easier home use and a more convenient dosing regimen will result in improved compliance, thereby reducing the occurrence of micro-bleeds into the joints (leading to premature joint degradation), avoidance of vascular damage by high-volume intravenous dosage and a smoother and more consistent plasma concentration

profile, giving a better prediction of the therapeutic benefit of these factors over time, benefitting patients and caregivers alike.

-Ends-

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About Pro Bono Bio Group plc

Pro Bono Bio Group plc ("PBB") is an international healthcare company, which partners with leading scientists, eminent physicians and specialist service providers, to ensure we have access to the best talent available to develop products that target key unmet medical needs. PBB's approach is designed to create and bring to market important new therapies which will improve the lives of patients worldwide. Pro Bono Bio launched its first medicine, FLEXISEQ™ for the treatment of pain associated with osteoarthritis in 2012 in Germany. Dermatology products, ROSSOSEQ and EXOSEQ, are scheduled to launch later this year.

About Haemophilia

Haemophilia A is the genetic disorder which causes an absence of the naturally occurring blood Factor VIII. Protein replacement therapy can be prophylactic (75%+ of patients in Western markets) or in response to bleeding events (greater in developing markets). The value of the global market for Factor VIII products in 2010 was circa $5bn. Haemophilia B is the genetic disorder which causes an absence of the naturally occurring blood Factor IX. Protein replacement therapy can be prophylactic (75%+ of patients in Western markets) or event-driven (greater in developing markets). The value of the global market for Factor IX products in 2010 was circa $1bn. Factor VIIa is needed as a substitute for Factor VIII when some (circa 30% of) haemophilia A patients develop an immune response to injected Factor VIII, thereby limiting its effectiveness. It is also used for the acute treatment of bleeding associated with major trauma and in some surgical settings. The value of the global FVIIa market in 2010 was estimated at circa $1.6bn.