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RESEARCH AND INNOVATION DG

PROFNAIT
Novel prophylaxis against FNAIT

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FINAL REPORT

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Final publishable summary report

for PROFNAIT (305986)

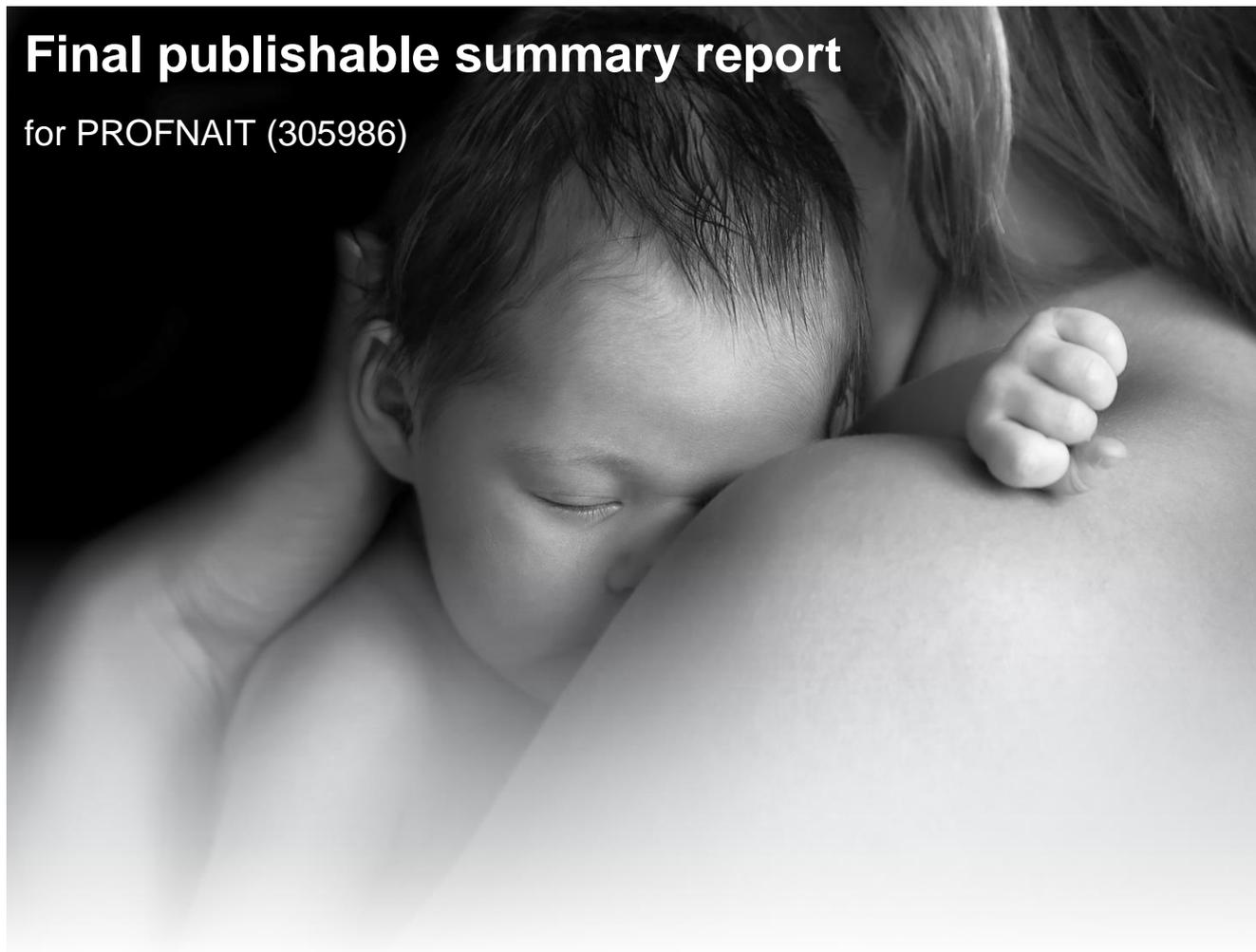


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4.1 Final publishable summary report

Executive summary

PROFNAIT is a European Union-funded consortium (www.profnait.eu) consisting of eleven Northern European hospitals, blood banks and companies, which aim to prevent 1,000 cases per year in EU and the US of potentially lethal or disabling internal bleeding in at-risk babies due to fetal and neonatal alloimmune thrombocytopenia (FNAIT). In spite of FNAIT being a rare condition, 13 leading EU and US medical societies in the fields of obstetrics and gynaecology have expressed their support of the PROFNAIT project and confirmed the unmet medical need in FNAIT.

The FNAIT prophylaxis PROFNAIT set out to develop, tentatively named NAITgam, must be manufactured from human plasma donated by women who has developed a certain antibody (immunoglobulin). Many of these women are mothers to FNAIT babies and the partners in PROFNAIT collaborated with the patient organization Naitbabies on recruiting their members as plasma donors. In parallel, thousands of existing plasma donors were screened to identify even more women who could donate this rare type of plasma. The identified donors were subsequently referred to one of the blood banks participating in PROFNAIT or to one of 50 authorized plasma collection sites in the US. In total, close to 1,000 plasma donations were made and a total of 650 litres of plasma were collected. It is estimated that more than 10,000 doses of NAITgam can be manufactured from the collected plasma.

The manufacturing and clinical development of NAITgam were discussed with the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and the German Paul-Ehrlich-Institut (PEI) to ensure agreement on fundamental safety and efficacy questions. The agencies expressed strong support of the project and agreed that the generally excellent safety of plasma-derived hyperimmune drugs like NAITgam and the challenge of identifying study subjects in this orphan condition justified a relatively limited development program consisting of a phase 0 study control study, a phase 1/2 dose-finding study and a single pivotal phase 3 study.

PROFNAIT consortium successfully completed the phase 0 study, which aimed to determine the natural rate of elimination transfused platelets. In the phase 1/2, it will be investigated if NAITgam is able to accelerate the elimination of a certain type of platelets, which simulate incompatible fetal platelets, and thereby presumably prevent the mother from being immunized and subsequently attack her foetus' platelets. The phase 1/2 study will also be used to establish the dose to be used in phase 3.

Many of the European academic and medical experts in FNAIT were partners in PROFNAIT, and a numerous peer-reviewed articles were published during the project. The project was also strengthened on the business side by the completion of US market research, a comprehensive health-economic study geared towards UK NICE and US Medicaid and a health-policy "roadmap" project that mapped the US stakeholders involved with the publication and implementation of new clinical guidelines on general testing pregnant women to identify those at risk of FNAIT and in need of NAITgam.

PROFNAIT created a strong basis for further development of NAITgam and future prevention of FNAIT, and many of the partners will continue to be involved with the project after the completion of PROFNAIT.

Summary description of project context and objectives

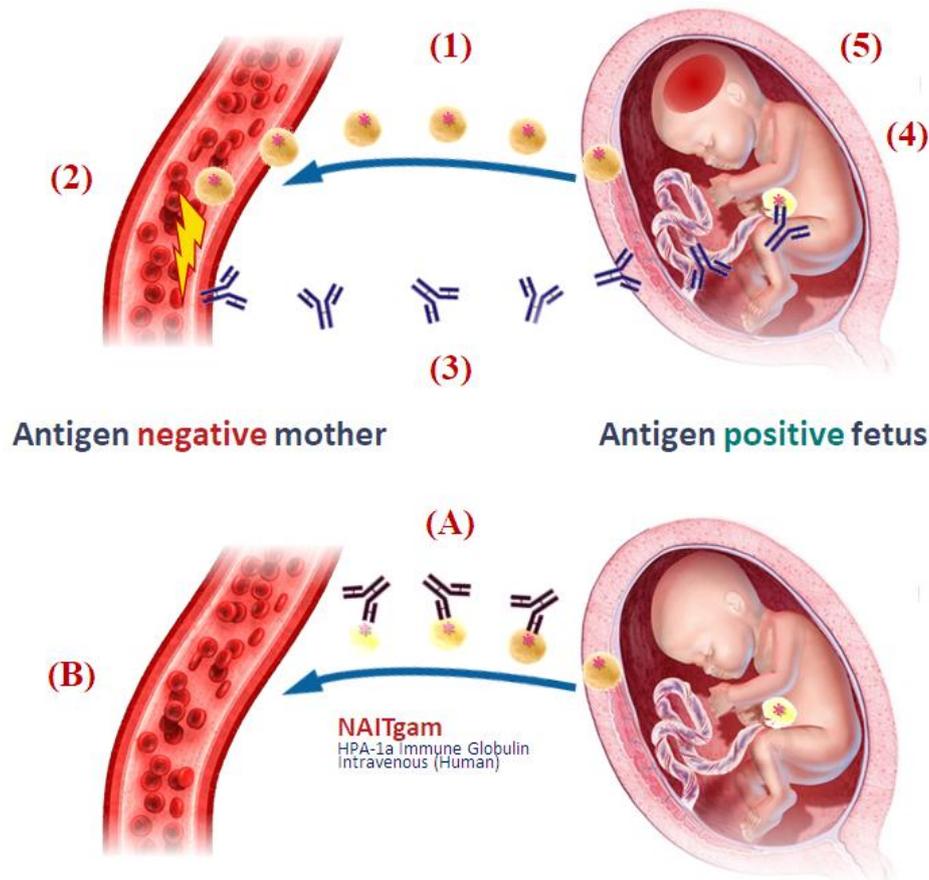
FNAIT– For more than 400 years, physicians and midwives have known about the clinical condition we today call haemolytic disease of the foetus and newborn (HDFN). This condition is caused by maternal red cell alloantibodies traversing the placenta and marking foetal red cells for elimination by phagocytosis. A similar but much rarer condition affecting fetal platelets, today known as fetal and neonatal alloimmune thrombocytopenia (FNAIT), was discovered much later, in 1957. Fetal thrombocytopenia, i.e. a low concentration of platelets, which are the cells that help stop bleedings, is seen in 1-3% of newborns and is associated with a variety of conditions, such as prematurity, infections, thrombosis, and certain congenital disorders. Among the severe cases of neonatal thrombocytopenia with platelet counts less than $50 \times 10^9/L$, approximately 25% are caused by FNAIT. Thus, FNAIT-related thrombocytopenia occurs in around 1 in 1,000 newborns while severe thrombocytopenia affects around 1 in 2,000 newborns. The clinical consequences of the newborn's low platelet count span a continuum, from no symptoms, to petechia, mucosal bleedings, hematomas, retinal bleedings, and intracranial haemorrhage (ICH), which may lead to intrauterine death or lifelong disability. The incidence of FNAIT-associated ICH is estimated to be around one of 10,000 newborns. As the total number of live births in the EU is around 5.3 million per year, it is assumed that the number of cases with ICH or stillbirth due to FNAIT is around 500 per year.

FNAIT management today–The management of FNAIT today is challenged by two major issues:

- 1) Pregnant women at risk of causing FNAIT in their foetus are not identified because the required testing, analogous to routine RhD-typing of pregnant women, is not performed. Appropriate testing would enable identification of the 0.5% of all pregnant women who are at highest risk of causing FNAIT in their foetus. Today, manifestations of FNAIT is the only means of diagnosis, and FNAIT is too often discovered too late to prevent the irreversible damages caused by this condition.
- 2) There is no approved or satisfactory treatment available. If a woman is known to have developed antibodies to foetal platelets, because she has already given birth to an FNAIT child, and if she becomes pregnant again, the obstetrician will have limited means with which to mitigate the risk of FNAIT in this subsequent pregnancy. In lack of better options, very high doses (in Europe typically 0.5-1.0 gram/kg/week) of intravenous immunoglobulin (IVIg), with or without corticosteroids, are commonly administered in an attempt to increase the fetal platelet count. However, the efficacy of this treatment strategy has never been tested against placebo in a randomized controlled trial (RCT), there is conflicting evidence on its efficacy in FNAIT, IVIg is not approved for this use, and the costs per pregnancy can easily exceed €100,000.

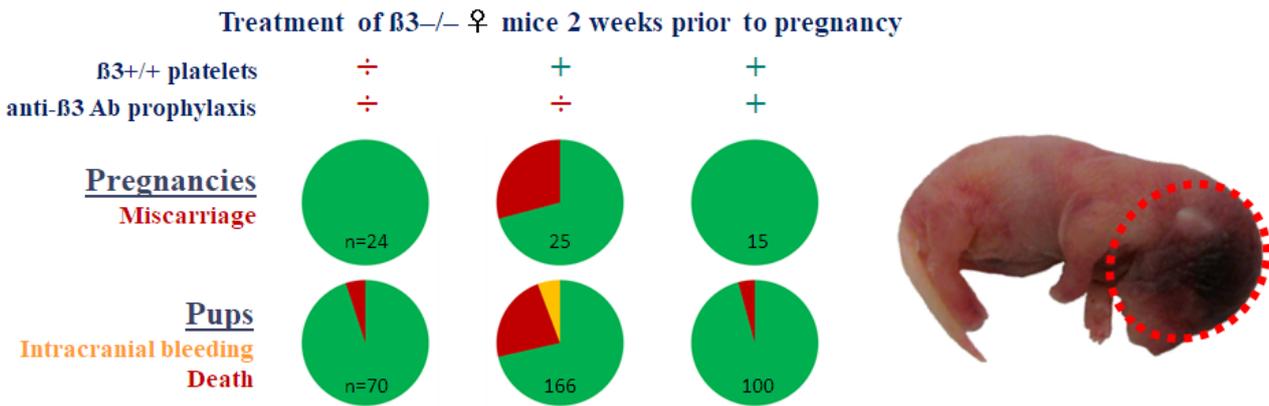
Unmet medical need–Clearly, the management of FNAIT today is hampered by both lack of testing and lack of medications with proven effect in prevention or treatment of FNAIT. Being a rare disease, severe FNAIT affects a relatively small number of foetuses and infants but the consequences of the condition can be absolutely devastating; just ask any of the members of the Naitbabies patient organisation.

An opportunity to prevent FNAIT –As mentioned, FNAIT and HDFN are both believed to be caused by alloimmunisation of mothers, who lack a certain platelet antigen. After a foetal-maternal bleeding, these mothers are exposed to the foreign antigen on the surface of the platelets and this initiates an immune response in the mother (*see upper panel in the figure below*). The common mechanism by which FNAIT and HDFN are caused also points to a common medical solution to preventing the conditions.



Development and prevention of FNAIT. Upper panel: During birth, blood from a foetus may be transferred to the mother (1) and cause the mother to develop allo-antibodies if the mother is HPA-1a negative and the HPA-1a antigen is expressed on the surface of the foetus' platelets (2). In a subsequent pregnancy, these antibodies may traverse placenta to the foetus during pregnancy (3) and cause destruction of the foetus' HPA-1a positive platelets (4). With few platelets, the foetus may be unable to stop spontaneous bleeding, the worst being bleeding in the brain (5), which can cause life-long disability or intrauterine death. Lower panel: Similar to anti-RhD therapy, the development of anti-HPA-1a antibodies may be prevented by injection of purified immunoglobulin containing hyperimmune anti-HPA-1a immunoglobulin (**NAITgam**). NAITgam binds HPA-1a positive platelets that have passed to the mother from the foetus (A) and the bound platelets are cleared from the bloodstream before the mother develops allo-antibodies to this antigen (B). Hence, NAITgam may prevent a subsequent foetus or newborn from having their platelets destroyed by maternal anti-HPA-1a antibodies

Since the mid-sixties, the development of maternal antibodies against RhD and HDFN have been very successfully prevented by treating RhD-negative pregnant women with anti-D hyperimmune immunoglobulin (e.g. RhoGAM) purified from plasma donated by RhD-immunised donors. Anti-D will attack any RhD-positive foetal red blood cells that have entered the mother's blood stream and cause them to be eliminated quickly and before her immune system has time to develop an immune reaction to the antigen. Similarly, a preparation of hyperimmune anti-HPA-1a immunoglobulin (IgG) may be used to quickly eliminated HPA-1a positive foetal platelets in a pregnant woman's or new mother's blood stream and prevent her from being immunised (*see lower panel in the figure above*). Furthermore, both anti-D preparations and anti-HPA-1a IgG preparations are or will be prepared by extracting total IgG from plasma provided by donors who are known to be RhD-immunised or HPA-1a-immunised (e.g. mothers to FNAIT babies), respectively. Standard plasma collection and drug manufacturing processes, which are approved by the European Medicines Agency (EMA) and the US



Prevention of FNAIT in a mouse model. A study in mice showed that risk of FNAIT, caused by transfusion of the mice with incompatible platelets, can be reversed by co-administration of an antibody that attacks the transfused platelets and cause them to be eliminated quickly. Left: Outcomes of normal pregnancies. Middle: Outcomes after transfusion of the mice with platelets and no prophylaxis. Right: Outcomes after transfusion of the mice with platelets and treatment with the prophylaxis.

Food and Drug Administration (FDA), already exist. Because the only difference between anti-D and NAITgam will be the selection of donors of the plasma, NAITgam can be anticipated to be as safe as anti-D.

In vivo model of FNAIT prophylaxis—A study in mice further supported the belief that FNAIT may indeed be prevented using the approach used for preventing HDFN. The scientific founders of the PROFNAIT coordinator Prophylix Pharma conducted a preclinical study in a murine model of FNAIT (figure above). In this model, mouse anti-platelet antibodies were injected to cause rapid elimination of transfused incompatible mouse platelets. By inhibiting the immunisation using this prophylactic approach, the platelet counts in the pups were significantly increased compared to pups born from mice receiving only incompatible platelets. Furthermore, pregnancy outcome (incidence of intracranial haemorrhage, miscarriage and dead-born pups) was reduced to the level seen in normal controls. This work conceptually proved that prophylactic administration of anti-platelet antibodies may prevent the development of FNAIT.

Objectives of PROFNAIT

The PROFNAIT project aimed at developing a first-in-class orphan drug, a human plasma-derived immunoglobulin G preparation named NAITgam, for the prevention of FNAIT. More specifically, the overall objective of PROFNAIT was to demonstrate proof-of-principle for the prevention of FNAIT using NAITgam and was pursued through the execution of work packages, each having its own sub-objectives:

Clinical trial material

- Develop and validate analytical methods
- Enter into plasma supply agreements with plasma collection organisations
- Recruit and qualify plasma donors and collect plasma for NAITgam manufacture
- Manufacture GMP-compliant clinical trial material

Clinical development

- Obtain support from EMA and FDA for the clinical development plan
- Develop and validate analytical methods

- In a phase 0 trial, determine the half-life of transfused platelets in the absence of NAITgam
- In a phase 1/2 trial, determine:
 - o the half-life of transfused platelets in the presence of NAITgam
 - o the safety and tolerability of a single i.v. dose of NAITgam
 - o the pharmacokinetics of NAITgam

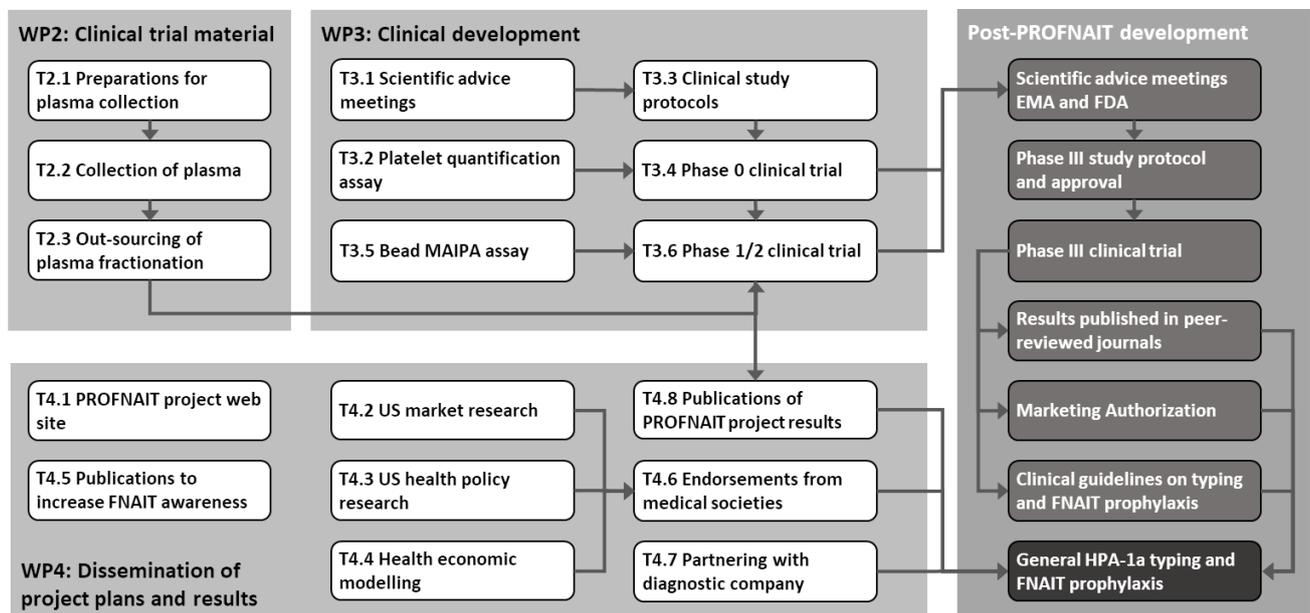
The results generated in the PROFNAIT project would support for a pivotal phase 3 study of NAITgam and for marketing authorisations for NAITgam by EMA and FDA after the completion of the project. NAITgam will be the first medication approved for FNAIT and the drug has already received Orphan Medicinal Product Designation from both the European Medicines Agency (EMA, EU/3/11/922) and the United States Food and Drug Administration (FDA, 06/27/2013), as well as designated by the FDA as a drug for a Rare Paediatric Disease.

Main Science and Technology results

The PROFNAIT project yielded significant results within a spectrum of areas all related to the manufacture, development, approval and commercialisation of the first-in-class drug NAITgam for the prevention of potentially disabling or life-threatening paediatric condition FNAIT. In addition to WP1 Project Management, the activities in PROFNAIT were organized in the three Work Packages:

- WP2 Clinical trial material
- WP3 Clinical development
- WP4 Dissemination of project plans and results

Below, the results of PROFNAIT will be summarized and described in more detail and in the post-PROFNAIT activities are discussed in the section on the potential impact, main dissemination activities, and exploitation of results.



Work packages and Tasks in the PROFNAIT project. In addition to WP1 Project Coordination, the three work packages were: WP2 Clinical trial material, WP3 Clinical development, and WP4 Dissemination of project plans and results. To the right is shown a number of activities that are foreseen to be completed after the conclusion of PROFNAIT.

WP2 Clinical trial material

Summary of key results

- Completion of Quality System and Quality Agreements with all involved parties regulating testing and handling of all plasma;
- Establishment of appropriate assays for testing of donor plasma and completion of the testing programme for the collected plasma;
- Establishment of sizable European and US networks of authorised HPA-1a plasma collection centres by PROFNAIT partners and in partnerships with three US plasma collection services;
- Recruitment of 70 (EU) and 25 (US) female HPA-1a plasma donors by PROFNAIT partners and in collaboration with the patient organisation Naitbabies, New York Presbyterian Hospital and BloodCenter of Wisconsin;
- Identification of 10 female HPA-1a-immunized US high-frequency plasma donors through screening of 8,000 donor samples;
- Collection of 140 litres (EU) and 500 litres (US) high-potency HPA-1a plasma from HPA-1a immunized female donors;
- Identification of 30 HPA-1a-negative male US high-frequency plasma donors through screening of 2,000 donor samples;
- Collection of 250 litres of “dilution plasma” from the male HPA-1a-negative plasma donors;
- Contracting of shipping and storage of plasma collected in the US to validated cold chain and warehouse.

T2.1: Preparations for plasma collection

Safety considerations

Transfusion-Related Acute Lung Injury (TRALI) is a rare but serious condition that can occur in patients receiving blood components or drugs containing antibodies against Human Leukocyte Antigens (HLA) and/or Human Neutrophil Antigens (HNA), and where these antibodies bind to the cognate antigens on the patient’s neutrophils.¹ It is extremely rare that healthy individuals receiving a blood product or a blood-derived drug product develop TRALI. Even so, all donors were carefully selected in order to ensure very low levels of free HLA and the absence of HNA antibodies in the plasma pool that constitutes the starting material. The analysis was performed at Aalborg University Hospital laboratory that is accredited according to DS/EN ISO 15189:2013. The laboratory further developed the anti HLA-assay in order to perform semi-quantification of detected anti-HLA antibodies.

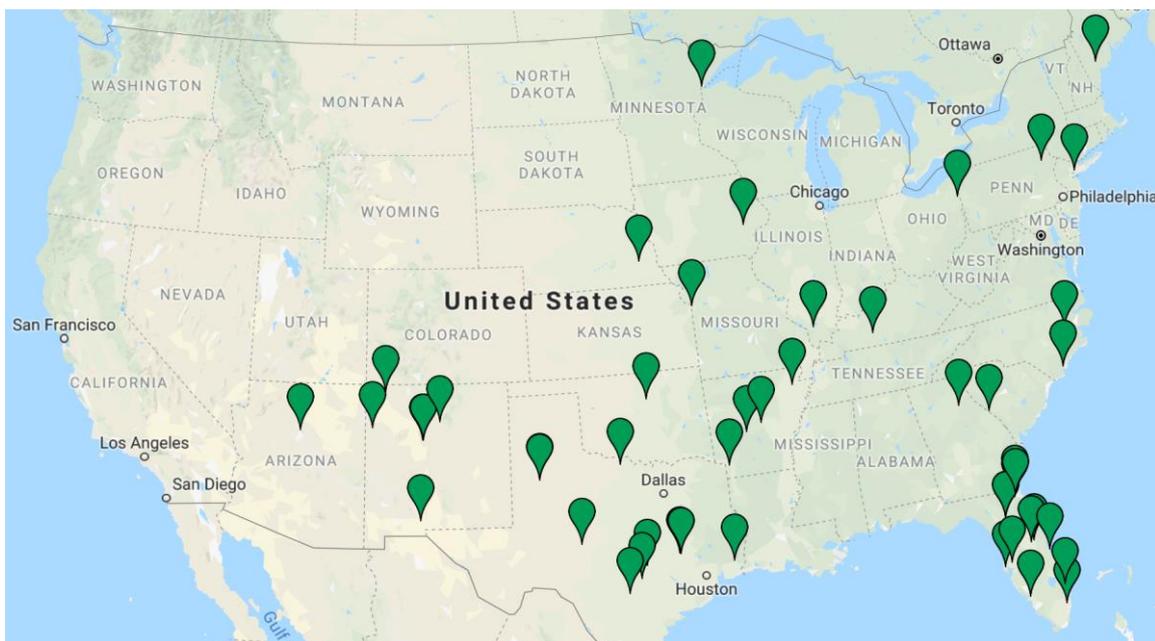
Further, it could be hypothesised that anti-HPA-1a administered to the mother after delivery of an HPA-1a positive child could bind to HPA-1a positive foetal platelets that have entered the mother’s blood, and that these antibody-coated foetal platelets will be phagocytosed or “eaten” by APC in the spleen. This process is also assumed to be immunologically quiet. However, NAITgam could potentially promote an immune response against HPA-1a instead of preventing HPA-1a-immunisation.

For this reason, we developed and validated (according to ICH-Q2) an assay for detecting platelet-activating HPA-1a antibodies in the plasma from potential donors. Fortunately, platelet-activating HPA-1a antibodies could only be detected in one individual. This donor was excluded from the donor program.

¹ Bux J, Sachs UJ. The pathogenesis of transfusion-related acute lung injury (TRALI). *Br J Haematol.* 2007 Mar;136(6):788-99.

As NAITgam will be manufactured from plasma collected from HPA-1a-immunised women of various blood groups, including women of blood group O, the pool of plasma that will constitute the starting material for the manufacture of NAITgam will also contain IgG antibodies against blood groups A and B. The safe amounts of anti-A and anti-B that can be administered in one dose of NAITgam was calculated based on the permitted amounts of anti-A and anti-B in human immunoglobulin for intravenous use. The calculated thresholds were supported by the German Paul-Erlich-Institut, and appropriate safety measurement will be included in the phase 1/2 trial. All donors' anti-A and anti-B IgG levels were measured to make sure that the plasma pool used for NAITgam would result in a drug product with far less anti-A and anti-B than permitted by the Paul-Erlich-Institut. Thus, NAITgam is likely to be safe and unlikely to cause haemolysis or acute renal dysfunction/failure.

EU and US plasma collection networks



Plasma collection centres in the USA. In collaboration with existing suppliers of human plasma, PROFNAIT succeeded in establishing a network of 50 plasma collection centres that were authorised to collect plasma from immunised women for the manufacture of NAITgam.

NAITgam must be manufactured from a human plasma, which contains antibodies to the HPA-1a antigen on the surface of platelets from HPA-1a positive individuals. In practice, only women who have become HPA-1a immunised during or after a pregnancy (as previously described) have such antibodies and can donate the required plasma. These women are rare and extensive networks of authorised plasma collection centres must be established to enable a reasonable number of these women to donate their plasma at a centre located close to where they live.

In Europe, the PROFNAIT partners DRK, Oslo and Karolinska succeeded in establishing a wide network of authorised collection sites by engagement of their own blood banks. In the US, PROFNAIT contracted plasma collection to three established plasma collection organisations with a total of 50 participating plasma collection sites. A logistics firm was tasked with shipping and storing the collected plasma according to the required standards.

T2.2: Collection of plasma

Donor identification and recruitment

As mentioned, few women have been HPA-1a immunised in connection with a pregnancy and they are challenging to identify and recruit as donors of HPA-1a plasma. Hence, three strategies for donor identification and recruitment were employed in parallel:

Sign-up donors. This category of donors were FNAIT mothers who registered as prospective donors on the PROFNAIT project's web site (www.profnait.eu). Because of their disease history, these mothers know that they have the desired HPA-1a antibody in the blood. In close collaboration with the patient organisation Naitbabies (www.naitbabies.org), which has around 1,100 members primarily in the US, Europe and Canada, PROFNAIT was brought in contact with Naitbabies' members in the US but because many did not live close to the, at the time, limited network of plasma collection centres, not all of the registered Naitbabies mothers were able to donate.

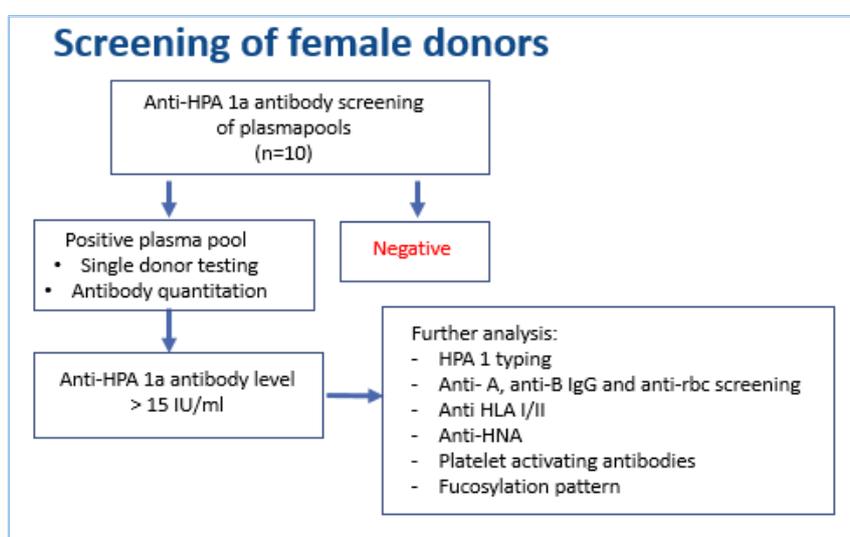
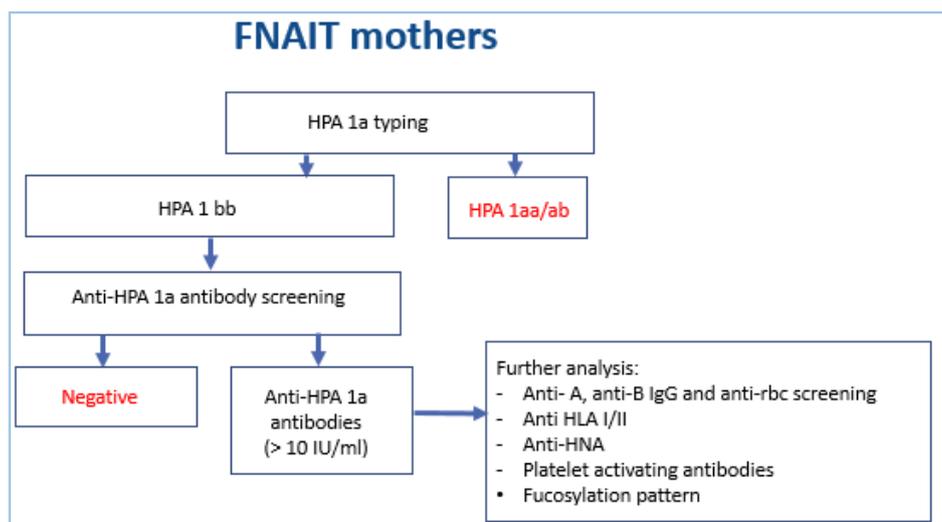
Referral donors. Some of the PROFNAIT partners, in particular Oslo and Karolinska, had previously been involved with FNAIT mothers and able to collect plasma and some donors were recruited directly by these partners. In addition, PROFNAIT established a collaboration with Dr. James Bussel at Weill Cornell Medicine in New York City (weill.cornell.edu). Dr. Bussel is a world-renowned pioneer in the management of pregnancies complicated by FNAIT and he has for three decades guided physicians across the US when they encountered cases of FNAIT. PROFNAIT entered into a two-year collaboration agreement with Weill Cornell on hiring a part-time assistant who Dr. Bussel permitted to reach out to his former patients. This assistant also managed most of the interactions with the sign-up donors in the US.

Screening donors. A prospective study of more than 100,000 pregnant women in Norway showed that around 0.15% of all newly pregnant women had already been HPA-1a immunised in a previous pregnancy. This means that a large group of women are HPA-1a immunised and may qualify as donors without knowing it. Therefore, PROFNAIT purchased a large number of plasma samples from female high frequency donors in the US, which UNN screened for the presence of HPA-1a antibody. While the costs of sampling and testing were substantial, this proved to be an effective strategy as these women are permitted to donate more than 1.5 litres of plasma per week.

Male donors were also screened by DRK and UNN in order to identify donors of "dilution" plasma. Because the level of HPA-1a antibody varies and NAITgam must be a standardised product, the plasma pool that is used as starting material in the manufacture of NAITgam must also be standardised. The dilution plasma, which is sourced from HPA-1a negative men, does not contain the HPA-1a antibody and can therefore be used to dilute the plasma pool to a standardised starting concentration.

Collection, testing and release of plasma

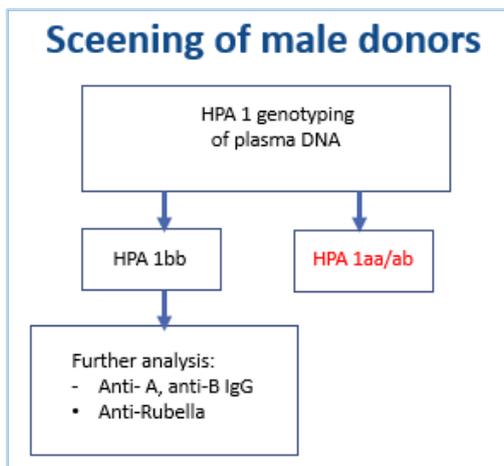
For the qualification of HPA-1a negative donors to be enrolled in the PROFNAIT donor program, different approaches were taken. This depended on if they were FNAIT mothers who volunteered (either through their physicians, NAITbabies.org or PROFNAIT web page), or female or male donors identified by screening. First of all; for qualification all donors had to be HPA-1a negative. Furthermore, to qualify as donors of HPA-1a plasma, the women had to have a minimum level of HPA-1a antibody in their plasma. Finally, for safety reason, all female donors were screened for a panel of other antibodies. The screening of female donors of HPA-1a plasma are outlined in the figures below. To make sure that the plasma was as safe as possible, male donors were also tested for anti-A and anti B IgG.



EU plasma: A total of 86 prospective female donors were identified in Germany, Norway and Sweden. The majority of donors were FNAIT mothers (n=69) referred to the program by their doctors, the rest were potential donors identified by screening of HPA-1a negative donors at German Red Cross. Utilization of EU plasma containing anti-HPA-1a IgG was highly desirable, but challenging, since only a few FDA-compliant manufactures would allow EU plasma into their facilities Further; US plasma can be used for making drugs for the EU market, but not the other way around.

US plasma: A total of 19,134 female plasma donors were screened for anti-HPA-1a antibodies and high titer donors were identified. In addition, a total of 125 women (FNAIT mothers) from across the US volunteered to donate. However, as discussed above, long travel distances to the plasma centres limited the number of donations from these volunteers. Collecting plasma from existing plasma donors was very efficient since high-frequency donors are permitted to donate 2 times per week and up to 60-80 litres per year.

Overview of plasma collected in PROFNAIT for NAITgam production	
Number of donors, n	54
Total volume, L	84 (EU), 765 (US)
Individual anti-HPA-1a antibody level, range	0-143
Anti-HPA-1a antibody level in plasma pool, mean IU/ml	20



Finally, DNA was isolated from plasma from a couple of thousands of male donors in the US, 30 HPA-1a negative male donors were identified and a total of 250 litres of dilution plasma were collected. Because 2% of male high-frequency donors can provide dilution plasma, this type of plasma is more readily available.

T2.3: Out-sourcing of plasma fractionation

The processes by which pharmaceutical plasma proteins, such as antibodies and albumin, are extracted from human plasma and made to become the active pharmaceutical ingredients in drug products are very important; the types and amounts of co-purified contaminants is critical for the safety profile of a plasma-derived drug product and the ability of the manufacturing process to preserve the biological activity of the plasma protein is critical for the efficacy. It is a saying in the industry that “*the process is the product.*” If the process is changed, the safety and efficacy data are no longer valid, and new clinical studies will be required. Therefore, subcontracting of manufacturing of plasma protein pharmaceuticals is in essence the beginning of a 10-20 year-long partnership. Furthermore, NAITgam will be a drug for the prevention of the rare to ultra-rare condition FNAIT, and the ideal manufacturer of NAITgam will be able to process small quantities of plasma (up to 500 litres), be compliant with both EMA and FDA guidelines and regulations and have similar immunoglobulin drug products on the market in EU and/or the US, proving that the manufacturer has a mature process and experienced staff, which can meet and maintain the high standards set for commercial-stage plasma drug products. Hence, a third party manufacturer of plasma-derived pharmaceuticals must be a good match from a business perspective as well as from a technical perspective.

The subcontracting of manufacturing of NAITgam did prove challenging and a number of options were explored before a highly qualified and motivated manufacturer was identified. At the time of completion of the PROFNAIT project, Prophylix is working intensely with a project team at the manufacturer on preparing the manufacture of a first batch of NAITgam in the spring of 2019.

WP3 Clinical Development

Summary of key results

- Completion of five scientific advice meetings with EMA, FDA and the German Paul-Erlich-Institut (PEI) with the following conclusions:
 - NAITgam will most probably have a benign safety profile.
 - No preclinical studies are necessary before testing NAITgam in humans.
 - Acceptance of platelet elimination as a surrogate endpoint for HPA-1a-immunisation.
 - Acceptance that an open-label observational study as the pivotal trial as an alternative to a randomised double-blind clinical trial.
 - Acceptance of focusing on HLA-DRB3*01:01 positive women in the pivotal phase 3 trial, i.e. the women with the highest risk of having their pregnancy complicated with severe FNAIT.
 - Acceptance that NAITgam could contain amounts of anti-A and/or anti-B up to 30,000 when expressed as administered volume multiplied by antibody titre.
 - Agreement on NAITgam phase 1/2 study protocol.
 - Agreement on outline of NAITgam phase 3 study.
- Validation of a sensitive assay for determining survival of transfused platelets.
- Validation of a highly sensitive anti-HPA-1a assay – the bead MAIPA assay.
- Completion of phase 0 trial with the following conclusions:
 - The mean (\pm standard deviation) terminal half-life of transfused platelets (without subsequent administration of NAITgam) is 2.3 days (\pm 1.4 days).
 - Technical and practical experience from the phase 0 trial has paved the road for flawless conduct of the phase 1/2 trial.

T3.1: Scientific advice meetings

FNAIT is a rare disease and for this reason there are many special challenges related to the development of a prophylactic treatment for this condition. Traditionally, new drugs are tested in randomised double-blind clinical trials where one study group is treated with the new drug and the other is treated with placebo. However, it would be immensely challenging to test NAITgam in a randomised double-blind clinical trial. Thus, it was essential to discuss with the regulatory authorities which alternatives trial design could be used for testing the efficacy of NAITgam. In 2014 briefing packages were prepared for a pre-IND meeting with the United States Food and Drug Administration (FDA) and for a Scientific Advice Meeting with the European Medicines Agency (EMA). The focus of these meetings where the design of the pivotal trial testing the efficacy of NAITgam in addition to a number of other essential questions related to the development of NAITgam. At this early stage there were no detailed plans for various stages of the development of NAITgam and FDA and EMA could therefore only give general advice on the development plan. The most important outcome of these two meetings can be summarised as follows:

- EMA and FDA agreed that NAITgam most probably would have a benign safety profile and that no preclinical studies, i.e. no animal studies, would be necessary before testing NAITgam in humans.
- The agencies acknowledged the challenges related to conducting a randomised double-blind clinical trial and approved that the pivotal trial of NAITgam could be an open-label observational study where the number of women who became HPA-1a-immunised were compared with historic controls.
- The agencies accepted that testing of how quickly NAITgam can eliminate HPA-1a positive platelets that have been transfused to HPA-1a negative male volunteers could be used as a

surrogate endpoint for NAITgam's ability to prevent HPA-1a-immunisation, and could be used for finding the appropriate dose of NAITgam to be tested in the phase 3 trial.

- The agencies accepted that the pivotal trial focused only on those women with the highest risk of becoming HPA-1a-immunised, i.e. women who were HPA-1a negative with a special tissue type (HLA-DRB3*01:01).

As NAITgam, will be manufactured from plasma collected from HPA-1a-immunised women of various blood groups, including women of blood group O, the pool of plasma, that will constitute the starting material for the manufacture of NAITgam, will also contain IgG antibodies against blood groups A and B. Thus, it is unavoidable that the recipients of NAITgam will also receive these antibodies in addition to the active pharmaceutical ingredient, i.e. the anti-HPA-1a IgG. As large doses of anti-A and anti-B can give rise to haemolysis in recipients of blood group A, B and AB it was essential do have the regulatory authorities' approval of the levels of anti-A and anti-B that could be expected in NAITgam. As the phase 1/2 trials would be conducted at the Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Project Group Translational Medicine and Pharmacology (FI) in Frankfurt, Germany, the regulatory agency that should eventually approve the clinical trial application would be the Paul-Ehrlich-Institut (PEI). Therefore, we requested a Scientific Advice Meeting with PEI which were held in February 2014. The primary outcome of this meeting was PEI's acceptance of our line of reasoning regarding the upper acceptable levels of anti-A and anti-B in NAITgam.

In 2018 the clinical development plan had matured. The phase 0 trial was running at FI, a protocol for the phase 1/2 trial had been finalised and a near final draft of the protocol for the phase 3 trial was available. Before initiating the phase 1/2 trial and later the phase 3 trial it was essential to have the regulatory agencies' approval of our plans. For this reason, we requested new meetings with EMA and FDA, which took place in July 2018. The primary outcome of these meetings were as follows:

- EMA accepted the proposed phase 1/2 trial, i.e. the design, the number of individuals, the endpoints etc.
- EMA accepted that the number women in the phase 3 trial who become HPA-1a-immunised could be compared with that 8.4 %, which was considered as a reasonable point estimate of the HPA-1a-immunisation risk in an untreated population of HPA-1a negative/HLA-DRB3*01:01 positive women who have given birth to an HPA-1a positive child.
- EMA agreed that the appropriate time for determination of HPA-1a-immunisation status in the phase 3 trial is 10 weeks postpartum.
- EMA accepted the proposed phase 3 trial, i.e. the design, the number of individuals, the endpoints etc.

Unfortunately, we did not obtain clear answers to our questions from the FDA. Instead, the FDA awaited submission of an IND and asked us to provide the rationale for our viewpoints in this document.

In all, we have had a series of very useful meetings with the regulatory authorities. These meetings have contributed to maturation of the development plan, and today, we are very well prepared for executing the clinical trials.

T3.2: Platelet quantification assay

As explained above, both EMA and FDA accepted that we use NAITgam's ability to eliminate HPA-1a positive platelets transfused to HPA-1a positive individuals as a surrogate endpoint for HPA-1a-immunisation and for finding the dose to be tested in the phase 3 trial. The dose of transfused platelets would be equivalent to the number of platelets present in 30 mL of foetal whole blood, i.e. 10×10^9 platelets. The percentage of transfused platelets, after transfusion of this small dose of platelet, would be less than 1 % of all circulating platelets. Hence, it was necessary to develop and validate an assay that could be used for following the survival of this very small dose of transfused platelets.

The standard method used for determining platelet survival has traditionally been based on transfusion of radioisotope-labelled platelets followed by determining the radioactivity of blood samples collected at different time-points after transfusion. There are ethical issues related to transfusion of radioisotope-labelled platelets to healthy subjects, and the method has several technical pitfalls. For these reasons, a newly developed flow cytometry-based method was used for determining platelet survival/elimination. As HLA class I antigens are expressed on platelets, differences in the HLA antigens between platelet donor and recipient were used to distinguish transfused platelets from endogenously produced platelets. Thus, platelet donors positive for HLA-A2 and/or HLA-A9 were intended for recipients negative for these HLA-antigens.

The flow cytometry-based method was optimised and tested on a number of mixtures of whole blood collected from HLA-A2 and/or HLA-A9 negative individuals and platelet rich plasma from HLA-A2 and/or HLA-A9 positive individuals. The mixtures were prepared so the percentage of HLA-A2 and/or HLA-A9 positive platelets were around 1 % and lower. The validation of this method was performed on such mixtures of whole blood and platelet rich plasma. The method was validated for levels of transfused platelets down to 0.015 % of the total platelet population.

T3.3: Clinical study protocols

The survival of transfused platelets without administration of NAITgam was examined in the phase 0 trial. The trial was conducted by FI in association with DRK. The protocol for this trial was prepared in the autumn of 2017 and submitted to PEI and the Committee for Medical Research Ethics at Goethe University, Frankfurt, for approval. The protocol was approved and the trial was started in April 2018. Up to 24 individuals could be recruited for the phase 0 trial. The trial would be terminated when evaluable data were obtained from 8 healthy subjects who had been transfused with 10×10^9 platelets.

A final study protocol for the phase 1/2 trial and a near final draft of the phase 3 trial was prepared during the spring of 2018 and submitted as parts of the briefing packaged for the Scientific Advice Meeting with EMA and the pre-IND meeting with FDA in July 2018.

The protocol for the phase 1/2 trial was almost identical with the protocol for the phase 0 trial except for the fact that NAITgam in the phase 1/2 trial would be administered 30 min. after termination of the platelet transfusion. Different doses of NAITgam would be tested in the phase 1/2 trial, and the lowest dose of NAITgam that can reduce the platelet half-life to around 6 hours would be selected as the dose to be tested in the phase 3 trial.

The phase 3 clinical trial will take place after termination of the PROFNAIT project. This trial will enrol 135 HPA-1a negative, HLA-DRB3*01:01 positive women who have given birth to an HPA-1a positive child. NAITgam will be administered hours to these women 6 hours after delivery of an HPA-1a positive child. All women will be examined for HPA-1a antibodies 10 weeks postpartum. The number of women from the phase 3 trial who become HPA-1a-immunised will be compared with a point estimate of the risk of HPA-1a-immunisation in an untreated population.

T3.4: Phase 0 clinical trial

Preparation of the phase 0 trial began late summer 2017. A number of PROFNAIT partners were engaged in this trial. The individual partners' main roles can be summarised as follows:

- Prophylix: Preparation of study protocol.
- FI:
 - Study site.
 - Recruitment of study subjects.
- DRK:
 - HLA typing of potential study subjects and platelet donors.
 - Provision of platelet concentrates for the study.
 - Analysis of survival of platelets transfused to study subjects.
- Larix: Coordinator of the trial.
- UNN and Oslo provided technical guidance related to
 - preanalytical handling of samples to be analysed for transfused platelets, and
 - optimisation of the analysis for determination of platelet elimination.

The protocol for the phase 0 trial was submitted for evaluation by PEI and the Committee for Medical Research Ethics at Goethe University, Frankfurt, early December 2017. The protocol was subsequently adjusted according to comments from both these two bodies. The first subject was transfused with platelets on April 17th, 2018. Detection of the very small number of platelets turned out to be more difficult than anticipated. For this reason, the dose of transfused platelets was increased to 20×10^9 platelets, i.e. a doubling of dose we initially planned to transfuse. In addition, telephone conferences, as well as a two-day on-site meeting in Frankfurt in June 2018, were conducted to improve the sensitivity of the assay for determining survival of transfused platelets.

As part of the feedback from the Scientific Advice Meeting from EMA, we were requested to reduce the transfused platelet dose from 20×10^9 platelets to 10×10^9 platelets as originally intended. Due to the considerable efforts put into optimising the method for determining survival of transfused platelets, we were eventually able to follow the elimination of platelets in 8 study subjects over a 5-day period.

All together 23 study subjects received a platelet transfusion. We obtained evaluable results from 6 individuals dosed with 20×10^9 platelets and from 8 individuals dosed with 10×10^9 platelets. The results from the remaining 9 study subjects were unfortunately not evaluable for various technical reasons.

The mean (\pm standard deviation) terminal half-life of transfused platelets in the subjects who were transfused with 10×10^9 platelets was calculated to 2.3 days (\pm 1.4 days). In a previous study from the PROFNAIT partner Oslo, the half-life of transfuse platelets was 2.0 days for platelet concentrates that were between 5 to 72 hours old ($n = 5$) and 1.5 days for platelet concentrates that were between 73 and 148 hours. In another study, platelet survival was examined in two patients with Glanzmann's thrombasthenia and Bernard Soulier Syndrome, and the half-life of platelets transfused these two patients were 2.6 and 4.6 days, respectively. Both these two studies used flow cytometry for determining survival of transfused platelets. Thus, the results obtained in the phase 0 trial are in accordance with previously published results.

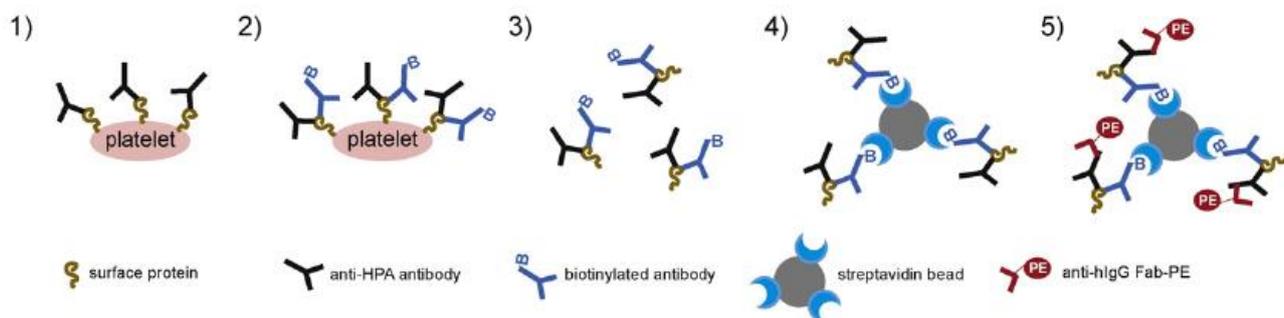
Beside determining the half-life of transfused platelets, we obtained the necessary technical experience with this challenging assay for measuring survival of very small amounts of platelets. This experience is essential for the next step of the development program where survival of transfused platelets will be determined after administration of NAITgam. Thus, we are confident that we will not experience the similar kind of technical problems in the phase 1/2 trial as we did in the phase 0 trial.

T3.5: Bead MAIPA assay

Karolinska University Hospital developed a modified MAIPA method with enhanced sensitivity in detecting antibodies against HPA-1a. The assay was further optimized and validated in the PROFNAIT project from a limit of detection of 0.4 IU/ml to 0.1 IU/ml.

The monoclonal antibody immobilization of platelet antigen (MAIPA) assay quantifies the antibodies (IgG) specific to human platelet antigen 1a (HPA1a) in plasma. HPA1a is a platelet alloantigen identified on the glycoprotein IIIa molecule (also known as CD61 or Integrin β_3) found on the platelet cell membranes of most humans. Serial dilutions of the reference standard, controls and test samples were separately incubated with HPA1a platelets. The targeted HPA1a antibodies (anti-HPA1a IgG) in the different sample/standard dilutions will bind to the HPA1a antigen site on the platelet membranes' glycoprotein IIIa (GPIIIa) molecules. Following a cell wash step, monoclonal antibodies specific to a different epitope (other than the HPA1a) on the GPIIIa are added to the platelet preparations. The monoclonal antibodies act as a primary capture antibody that indirectly binds with the previously formed HPA1a antigen-antibody complexes. Using biotinylated monoclonal antibodies, streptavidin coated beads and detection by flow cytometry, the bead MAIPA gave superior resolution (10-fold higher) for detection and quantification of anti-HPA 1a antibodies. The bead-MAIPA were validated according to ICH guideline (ICH-Q2)

This study was successful in verifying the specificity, accuracy, precision, linearity and robustness of the bead-MAIPA method and considered suitable for its intended use; dose finding in samples in clinical phase I/II trial. And detection of immunization (enrolment and evaluation of immunization status postpartum) in the phase III study.



Schematic figure of the bead-MAIPA

T3.6: Phase 1/2 clinical trial

As explained above the protocol for the phase 1/2 trial was prepared during the spring of 2018 and the phase 1/2 trial was discussed with EMA during the Scientific Advice Meeting in July 2018. However, shortly after this meeting, we were informed by the company, which was going to manufacture NAITgam late summer 2018, that the manufacture of NAITgam would be delayed for more than one year. Without a drug it was not possible to start clinical testing. Consequently, the PROFNAIT Consortium did not manage to fulfil the task of completing the phase 1/2 trial. Nevertheless, completion of the phase 1/2 trial as well as the phase 3 trial will take place after termination of the PROFNAIT project.

WP4 Dissemination of project plans and results

Summary of key results

- Publication of 32 pre-reviewed papers on FNAIT
- 14 international, 9 national and 7 local presentations on FNAIT
- Addressed 13 medical societies in obstetrics and gynaecology to gage unmet need in FNAIT and support of general HPA-1a typing and FNAIT prophylaxis
- Completion of US market research
- Completion of US health policy research
- Completion of health-economic modelling
- Building and publication of a project web site (www.profnait.eu)

T4.1: PROFNAIT project web site

A project web site www.profnait.eu was published early in the project to provide information about FNAIT and the PROFNAIT project but also to enable HPA-1a immunised women (FNAIT mothers) to sign up to donate plasma containing the critical HPA-1a antibody. Thanks to the strong backing of the Naitbabies patient organization (www.naitbabies.org) in particular, the recruitment of donors was highly effective and 125 women signed up on the PROFNAIT web site during the plasma collection campaign.

T4.2: US market research

As the US health care market is very complex with multiple public and private payers and providers, PROFNAIT initiated a study to improve the understanding of how the prophylaxis NAITgam would be received in this market. The study was performed by a market access analysis firm that is specialised in orphan drugs in involved 35 structured interviews of physicians, pharmacy directors and Medicaid specialists. Three of the main conclusions from the study were that:

- 1) The general awareness of and knowledge about FNAIT is low even among key stakeholders and that strong advocacy is needed,
- 2) The endorsement of the American Congress of Obstetrics and Gynecology, ACOG (in the form of clinical guidelines recommending HPA-1a typing of pregnant women and that an FNAIT prophylaxis is given to women at-risk of causing FNAIT) is important for the adoption of general HPA-1a typing of pregnant women and FNAIT prophylaxis, and
- 3) The required implementation of general HPA-1a typing of pregnant women should be promoted in collaboration with one or more of the major diagnostics players in the field.

The conclusions led to the further research performed in tasks 4.3 and 4.4.

T4.3: US health policy research

Because the US market research performed in Task 4.2 uncovered that key stakeholders were poorly informed about FNAIT, and because of the importance of the endorsement of ACOG, a Washington-based market research firm was tasked with mapping the stakeholders influencing the publication and/or the implementation of an ACOG guideline on HPA-1a typing of pregnant women and administration of FNAIT prophylaxis to mothers at-risk of being immunized. Following interviews with a number of the identified organisations, information needs, communication channels were also mapped. The study report also detailed ACOG's process and timeline for publication and revising clinical guidelines.

T4.4: Health economic modelling

In Task 4.6, a number of medical societies in the field of obstetrics and gynaecology were asked if they would endorse general HPA-1a typing of pregnant women and administration of an FNAIT prophylaxis to those at highest risk. While essentially all of these societies strongly supported the efforts of PROFNAIT, many made their support contingent on the cost-effectiveness of this new regimen for preventing and managing FNAIT.

A health-economic study was therefore performed to determine what total cost to society would make HPA-1a typing and FNAIT prophylaxis cost-effective vs. standard of care. A health-economic advisory firm was engaged to perform the analyses in collaboration with staff at Prophylix and independent experts specialised in the cost-effectiveness assessments performed by the UK NICE and US Medicaid. The economic model that was built is based on a decision-tree structure and the independent advisors took part in reviewing the relevant literature, the estimation of probabilities, building of the outcome models and in assigning probabilities and costs. The study concluded that HPA-1a typing and FNAIT prophylaxis highly cost-effective vs. standard of care.

T4.5: Publications to increase FNAIT awareness

A total of 32 publications in international pre-reviewed journals have been published in the whole PROFNAIT period. The publications range from basic immunological studies, such as T-cell response and development of a monoclonal anti-HPA 1a that can be used in diagnostic assays, method developments (e.g. bead-MAIPA, fetal HPA 1 typing), publications on calculation of risks and HLA DRB3*01:01 involvement. To studies on maternal anti-HPA 1a antibodies effects on trophoblasts, endothelial cells and angiogenesis in general, and fucosylation of maternal antibodies and FNAIT severity. And finally observational studies, literature reviews, suggested new treatment options and guidelines for clinicians.

In addition several presentations and lectures has been completed internationally (14 presentations), nationally (9 presentations) and locally (7 presentations), in addition to several lecture in clinical immunology and transfusion medicine for clinicians as well as presentation for investors.

T4.6: Probing of support from medical societies

We approached a large number of national medical societies to examine, to what extent clinical specialists such as obstetricians, paediatricians and maternal-foetal medicine specialist consider today's management of FNAIT insufficient. A briefing document was sent to the societies in which we explained about the PROFNAIT project and the endeavours of developing a new drug in class for the prevention of HPA-1a-immunisation and FNAIT.

We asked each society to answer the following two questions:

1. Does the society agree that today's treatment and prophylaxis of FNAIT is insufficient and that FNAIT represents an unmet medical need?
2. Given
 - a. that the pivotal clinical trials demonstrate efficacy of NAITgam,
 - b. that there are no clinically significant adverse effects associated with administration of NAITgam,
 - c. that there is a robust HPA-1a typing kit available at low cost, and
 - d. that there is a reasonable balance between the overall costs of preventing FNAIT and the improvements in health;

will the society support the implementation of general HPA-1a typing of pregnant women after marketing authorisation has been obtained for NAITgam?

The support we obtained was overwhelming, and the vast majority of the societies responded positively to both questions. As shown in the figure below, 13 medical societies endorsed the PROFNAIT project and the endeavours of developing a prophylaxis against HPA-1a-immunisation and FNAIT. It is also noteworthy that all the North American societies are very influential societies with a great saying when it comes to establishing new or revising current clinical guidelines in their respective countries. In Europe we also obtained support from the medical societies from the Scandinavian countries, the UK, the Netherlands, Germany and Spain.



Medical society endorsements. Medical societies who have acknowledged the unmet medical need in FNAIT and endorsed the PROFNAIT project’s endeavours to develop a prophylaxis against HPA-1a-immunisation, FNAIT and brain damage in fetuses and newborns.

Thus, we are convinced, that within a few years after licensure of NAITgam, HPA-1a typing will become an integral part of the current antenatal health care programme in both the EU and North America.

T4.7: Partnering with diagnostic company

As mentioned above, a key result of the US market research performed in Task 4.2 was the importance for Prophylix, as sponsor of NAITgam, to partner with a major diagnostics company that is involved in routine RhD typing of pregnant women today. Such a company would know the marketplace and be a great help in co-promoting HPA-1a typing of pregnant women.

It turned out that one of the major diagnostics companies deeply involved in large-scale RhD typing of pregnant women was contemplating developing and commercialising a test for HPA-1a typing of pregnant women. As the diagnostics company’s and Prophylix’s goals were highly synergistic, a formal partnership on licensing of an antibody and co-promotion of general HPA-1a typing of pregnant women was quickly established.

The potential impact, main dissemination activities, and exploitation of results

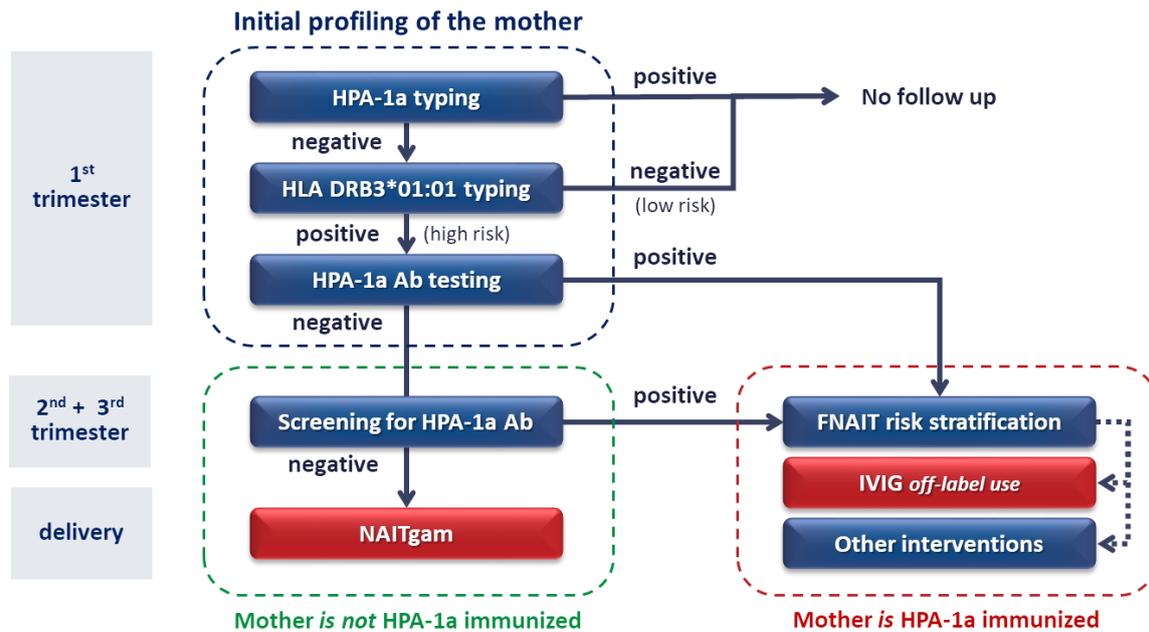
EMA, FDA and 13 medical societies in the area of obstetrics and gynaecology have acknowledged the unmet medical need in the rare but potentially chronically disabling or lethal paediatric condition, FNAIT. Today, women at risk of causing FNAIT in their babies are not identified because the required testing is not performed. The testing can easily be done, but is not performed, and nothing is done to minimise the potentially detrimental impact of FNAIT. Today, no treatment is available for preventing HPA-1a immunization of HPA-1a negative mothers, and today no approved or documented effective treatment is available to mitigate the effects of maternal HPA-1a immunisation. In lack of a better option, IVIG is widely used off-label to reduce the impact of FNAIT in subsequent pregnancies and that is done in spite of unproven effect, substantial side-effects and a cost in excess of €100,000 per pregnancy.

The project's potential impact on FNAIT health care

The partners in the PROFNAIT consortium set out to overcome these serious shortcomings in today's FNAIT health care by taking critical first steps towards fundamentally improving diagnosis and management of FNAIT, see table below.

Impact area	Today	Future
Diagnosis	A stillborn foetus or FNAIT in a potentially chronically disabled newborn.	Routine testing of all pregnant women in parallel to today's RhD typing. FNAIT risk stratification and optimal FNAIT risk mitigation throughout pregnancy in already immunised women.
Prophylaxis (mother <i>is not</i> already HPA-1a immunised)	None.	Prevention using NAITgam of HPA-1a immunisation of up to 750 cases per year of FNAIT-related intracranial haemorrhage and life-long disability or intrauterine death.
Therapy (mother <i>is</i> already HPA-1a immunised)	Off-label use of IVIG Early Caesarean section Platelet transfusion after delivery	Earlier detection of HPA-1a immunisation will enable utilisation of existing FNAIT risk mitigation strategies during the pregnancy.
Costs	Costs of IVIG Costs of neonatal brain damage, equivalent to cerebral palsy Stillbirths	Costs of testing Costs of NAITgam prophylaxis With time, reduced costs of IVIG and neonatal brain damage and fewer stillbirths

Most importantly, 750 cases per year of FNAIT-associated intracranial haemorrhage (ICH), which can result in life-long disability or intrauterine death, may be prevented to the benefit of the babies and the affected families. Although rare, a baby born with brain damage also represents a substantial economic burden to society and PROFNAIT has brought us one step closer to realising the International Rare Diseases Research Consortium (IRDiRC)'s goal to develop 200 new therapies and the means to diagnose most rare diseases by the year 2020. While we will not meet this deadline, PROFNAIT and the subsequent further development and approval of NAITgam will contribute to achieving IRDiRC's new goal 2, which is to get 1,000 new therapies for rare diseases approved in the decade from 2017-2027.



Comprehensive FNAIT prevention and management strategy. The vision of PROFNAIT is that all pregnant women are HPA-1a typed early in their pregnancy using the same blood sample that today is used for RhD-typing. The 2% of women who are HPA-1a negative will also be tested for HLA DRB3*01:01 type and presence of HPA-1a antibodies, indicating immunisation in a previous pregnancy. Depending on these test results, HPA-1a negative and HLA DRB3*01:01 positive women who are not immunised will be monitored for antibody development during pregnancy and given NAITgam after delivery, while the women who are already immunised will be offered FNAIT-risk mitigating healthcare during and after their pregnancy.

The vision of PROFNAIT extends well beyond prevention of FNAIT using NAITgam, see figure above. Identification of at-risk pregnancies already in the first trimester will enable physicians to provide optimal care for both women who are not already immunised, and who may benefit from NAITgam, but also for women who are already immunised and at risk of causing FNAIT in the baby they are currently carrying. If a pregnant women is found to be immunised, the risk of FNAIT will be assessed (e.g. based on the level of HPA-1a antibody in her blood) she can be offered personalised healthcare, such is IVIG therapy, early Caesarean section and platelet transfusion of the newborn.

While this comprehensive FNAIT management scheme may lead to increased use and costs of IVIG therapy short-term, because the number of already immunised women will remain high for years to come, the prevention of FNAIT, intracranial haemorrhage and life-long disability will also result in substantial cost savings. In the health-economic analysis performed in Task 4.4, the lifetime healthcare and social care costs of a severe case of FNAIT was assumed to be the same as the cost of cerebral palsy, EUR 150,000 to 700,000 per case. While severe FNAIT is rare, the health, emotional and economic costs of the condition are very substantial. It is a condition that can forever change the life of a baby and its family.

Dissemination of the project's results

The health-policy research performed in Task 4.3 clearly identified the need for comprehensive information about FNAIT. Even among key stakeholders such as regulatory authorities, governmental healthcare policy organisations and medical societies, the awareness of and knowledge about FNAIT is limited.

PROFNAIT, in many cases in collaboration with the Naitbabies patient organisation, began the major task it is to bring FNAIT and the PROFNAIT project to the attention of these stakeholders and to the attention of the relevant academic and medical societies.

As mentioned in the description of the work related to Task 4.5, a total of 32 publications in international pre-reviewed journals have been published, and FNAIT and PROFNAIT have been presented internationally (14 presentations), nationally (9 presentations) and locally (7 presentations). Furthermore, in Task 4.6 briefing packages about FNAIT and the efforts of the PROFNAIT consortium to develop an FNAIT prophylaxis were sent to a range of relevant medical societies. 13 key societies carefully evaluated to documentation and confirmed the unmet need and support of the PROFNAIT consortium's efforts to develop NAITgam and implement the envisioned testing and FNAIT prevention strategy. Finally, PROFNAIT have sought scientific advice from EMA, FDA and the German Paul-Ehrlich-Institut five times and have had very constructive interactions with these authorities. As sponsor of NAITgam, Prophylix will maintain an increasingly close dialogue with all of these stakeholders and continue to inform them about FNAIT, the prospect of preventing the condition and the development of NAITgam.

Exploitation of the project's results

The exploitation of the PROFNAIT project's results and implement the comprehensive FNAIT prevention and management strategy outlined above are contingent on the execution of a number of independent activities. Prophylix has an option to acquire the foreground developed in PROFNAIT and will be the sponsor of NAITgam going forward.

Manufacturing—The first step in the exploitation of the PROFNAIT project's results is to manufacture NAITgam. A first batch of NAITgam is scheduled to be produced in Q2-Q3 of 2019 and one or two additional conformance lots are anticipated to be required to document reproducibility of the process and obtain marketing authorisation for NAITgam.

Clinical studies—A clinical development plan for NAITgam was agreed with EMA and FDA, and a phase 2 dose-finding study is scheduled to be performed in Q1-Q2 of 2020 in collaboration with partners of the PROFNAIT project. This study will also establish proof-of-concept as NAITgam's capability to greatly accelerate the rate of elimination of incompatible, HPA-1a positive platelets will be documented. Subsequently, a single pivotal phase 3 study will be performed in 2021 using the dose selected based on the phase 2 study results. In this study, NAITgam will be administered to new mothers within hours after delivery and the rate of immunisation of these women will be compared to the natural rate of immunisation when no NAITgam is administered (12%).

Regulatory approvals—EU and US marketing authorisation applications summarising the CMC documentation and the results of the phase 2 and 3 studies will be submitted with EMA and FDA in 2022, possibly in the form of requests for conditional (EMA) and accelerated (FDA) approval.

Plasma procurement—While the collection of plasma is currently on hold because plasma for several batches has been collected, an expansion of the network of plasma collection centres, renewed donor identification and recruitment and restarting of plasma collections must be completed in preparation for the commercial phase and the anticipated much larger demand for product and plasma. Prospective new partners that can provide close to 100 additional collection sites have expressed interest in collecting HPA-1a specialty source plasma for the manufacture of NAITgam.

FNAIT testing—This activity area covers the development and commercialisation of the assays required to implement the comprehensive FNAIT prevention and management strategy shown above, as well as creating the demand for general HPA-1a typing of pregnant women through, in turn, the publication of phase 3 results in peer-review journals, publication of clinical guidelines on routine HPA-1a typing and FNAIT prophylaxis in the US, negotiations with national health authorities in Europe and

implementation of guidelines and policies. Close collaborations with key academic, clinical and healthcare stakeholders in both EU and the US, with the Naitbabies patient organisation, with providers of diagnostics hardware and services and with healthcare payers will be critical for rapid adoption of HPA-1a typing and FNAIT prophylaxis.

Contact details and project partners

Project website: www.profnait.eu

In the table below are listed the names and E-mail addresses of the contact persons from each of the PROFNAIT partners.

PROFNAIT partner	Contact persons	E-mail addresses
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4.2 Use and dissemination of foreground

The PROFNAIT project has provided an essential platform for further development of a treatment for the prevention of HPA-1a-immunisation and FNAIT. Sufficient plasma has been collected for the manufacture of two batches of NAITgam; the first batch scheduled to be manufactured in May 2019. In addition, conduction of the phase 0 trial has paved the way for the phase 1/2 trial, which will be the first-in-man trial of NAITgam. This trial is scheduled to start in the autumn of 2019. Finally, through scientific advice meetings with EMA, FDA and PEI, we have found a regulatory way for the development of NAITgam, which eventually lead to licensure of NAITgam within the shortest possible time frame. Thus, the development of NAITgam will continue despite termination of the PROFNAIT project.

The results of the clinical trials will not only be the basis for the regulatory dossier for licensure of NAITgam, but will also concurrently be presented at medical and scientific conferences, and published in peer-reviewed medical and scientific journals. Moreover, we will continue to increase the awareness of FNAIT by publishing up-to-date review papers on FNAIT. Our efforts of disseminating results of the clinical development of NAITgam and FNAIT in general, will not be limited to clinicians who are in charge of managing this condition: The close collaboration we have had for years with the patient organisation Naitbabies (www.naitbabies.org) will continue, and information about the progress regarding the clinical development of NAITgam will be presented in layman's words through Naitbabies network; particularly through their website.

As soon as the clinical results have documented NAITgam's efficiently in preventing HPA-1a-immunisation, we will approach a number of influential governmental and non-governmental organisations in North America, which views are essential for implementation of general HPA-1a typing and FNAIT prophylaxis in the US. These organisations, and their role in this process, have been clarified through task T4.3 of work package 4.

In parallel, we will initiate a dialogue with the most influential medical societies in Europe and North America and discuss, if it is time to revise the current clinical guidelines regarding FNAIT management. These societies have previously endorsed the endeavours of the PROFNAIT Consortium to develop a prophylactic treatment of FNAIT, and it is highly likely, that they would change the clinical guidelines when the results from the clinical trials have demonstrated NAITgam's efficacy. With the support from these medical societies we will approach the national health authorities and discuss if it is time to upgrade the current antenatal health care programme to also include HPA-1a typing and FNAIT prophylaxis. The question of performing HPA-1a typing of all pregnant women to identify women at risk has already been discussed by the national health authorities in Norway, Denmark, the UK and the Netherlands. The reason HPA-1a typing has so far not been adopted is due to the fact that there currently is no prophylaxis to offer women at risk of having their pregnancy complicated by FNAIT. Thus, when a successful completion of the development programme of NAITgam has removed this hindrance, we believe most Western countries will adopt general HPA-1a typing and FNAIT prophylaxis as part of their antenatal healthcare programme, which in turn will significantly improve the welfare of children at risk and their families.

Section A (public)

List of scientific (peer reviewed) publications and the list of dissemination activities is uploaded to the Funding and Tenders portal.

Section B

The List of applications for patents, trademarks, registered designs, etc. is not applicable

The exploitable foreground is uploaded to the Funding and Tenders portal.

4.3 Report on societal implications

The report is uploaded to the Funding and Tenders portal.