PROJECT FINAL REPORT

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Project acronym: MABSOT

Project title: Development of OPN-305 as an orphan drug for the treatment of Delayed Graft Function post solid organ transplantation

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FINAL PUBLISHABLE SUMMARY REPORT

1. EXECUTIVE SUMMARY

The primary aim of the MABSOT project was the development of OPN-305 (humanised anti-TLR2 monoclonal antibody) as an orphan drug for the treatment of Delayed Graft Function post solid organ transplantation. In order to achieve this aim the consortium selected six clinical centres, 2 in the UK, 1 in Belgium, 1 in the Czech Republic, 1 in The Netherlands and 1 in Spain that have a strong track record in transplantation research and clinical studies. The Clinical studies were further supported by Almac Diagnostics, UK and the project was managed by the Study Coordinator Opsona, Ireland with support from management company Euram, UK.

The project commenced on December 1st 2010 and concluded on September 30th 2014. A synopsis of the key study results from the MABSOT project is provided below.

WP1: Non clinical studies

Pivotal toxicology studies with OPN-305 in monkeys were successfully completed. OPN-305 was well tolerated in the monkey pivotal toxicology studies; there was no concern about the safety of OPN-305 in humans based on the non- clinical studies.

WP2: IMP Manufacture

IMP (Drug Product) for Phase I and Phase II clinical trials was successfully manufactured and drug product and placebo delivered to clinical trial centres.

WP3: In vivo efficacy studies of OPN-301 in murine models of acute and chronic rejection

Studies were performed in mice to examine the effect of blocking TLR2 signalling on chronic and acute heart rejection and chronic renal rejection post-transplant. InhbitingTLR2 was observed to have a significant effect on graft function in the chronic renal rejection model, little or no effect was observed in either cardiac rejection models.

WP4: Identification of endogenous TLR2 ligands associated with TLR2-mediated ischaemia-reperfusion injury.

Serum Amyloid A (SAA) was identified as an endogenous ligand of TLR2, however a positive correlation between SAA levels in the serum of renal transplant patients and delayed graft function was not observed.

WP5: Identification of Biomarkers for Kidney Damage and DGF

Two candidate biomarkers were identified, however a positive correlation between the levels of these biomarkers in the serum of renal transplant patient and delayed graft function was not observed.

WP6: OPN-305 Clinical Trials Phase I/II

Phase I clinical was successfully completed in healthy volunteers, no SAEs related to OPN-305 in Healthy Volunteers were noted. Three SAEs were considered possibly related to OPN-305 or placebo in Part A of the Phase II trial. Phase II in renal transplant patients commenced in Q42012 and Phase0 & Part A of the study were concluded in December 2012 and April 2014 respectively. Results from Part A of the study indicated a positive effect in patients that received an Extended Criteria Donor kidney and were treated with 0.5mg/kg OPN-305. Part B of the study which focuses on patients receiving ECD kidneys and treated with OPN-305 at 0.5mg/kg commenced in April 2015. However, as the MABSOT project did not receive an extension to the project duration the results from Part B will not be reportable under MABSOT

WP7: Dissemination & Exploitation.

National filing of the OPN-305 patent which provides cover for the use of OPN-305 irrespective of the disease application in 14 jurisdictions worldwide. The patent has now been granted in Australia, Europe, Mexico, New Zealand (parent and divisional patents), South Africa and the USA. The project has been disseminated through the project website, twitter account and at numerous national and international meetings

2. PROJECT CONTEXT AND OBJECTIVES

Project Concept

Several rare diseases, particularly those of genetic origin such as lupus and congenital heart defects, are associated with declining organ function as the disease progresses. The only treatment for these conditions is prolonged medical intervention and solid organ transplantation. Although solid organ transplantation is the best treatment for end-stage organ failure, there are a number of consequences associated with transplantation. One of these is delayed graft function (DGF) which has been particularly well described after renal transplantation. DGF essentially means that allograft function is not immediate and that life needs to be sustained while the allograft regains its function. In the case of renal transplantation DGF is defined as the need for dialysis within seven days of transplantation. DGF requires prolonged dialysis and hospitalisation, promotes allograft rejection and increases the likelihood of allograft failure.

DGF occurs in 21-50% of cases following deceased donor kidney transplantation and in ~6-10% of cases following living donor kidney transplantation. DGF is caused by ischaemia-reperfusion injury (I/R injury) and its severity varies depending on several factors among them; cold ischaemic time, warm ischaemic time, and donor age. Ischaemia is the period in which the transplant organ is deprived of a blood supply following removal from the donor. When the recipient patient receives the transplant organ blood supply is restored and this is known as reperfusion. The damage caused by I/R injury occurs through the immune mediated reactions in which the innate immune system plays a significant role. The Toll-like receptors (TLR) are of vital importance in the activation of both the innate and the adaptive immune system. In the kidney, the activation of TLR2 is of pivotal importance in mediating I/R injury.

Opsona Therapeutics has developed a novel antibody (OPN-305) which has received Orphan Medicinal Product (OMP) designation in Europe (EU/3/09/638) and Orphan Drug Designation in the USA (ODD: 11-3553) for use in the prevention of DGF post solid organ transplantation. The scientific basis of this development is the inhibition of TLR2-mediated ischaemic reperfusion injury which has a pivotal role in the pathogenesis of DGF and its sequelae.
While the initial indication for OPN-305 is renal transplantation the mode of action mediated via inhibition of TLR2-mediated I/R injury has implications for the wider use of the drug to treat other solid organ transplantation situations (i.e. heart, liver, lung etc) where I/R injury inevitably occurs.

Overall Project Objectives

1. Complete non-clinical testing (Milestone 1) and final IMP (Investigational Medicinal Product: also referred to as the Drug Product) manufacture, packaging, labelling and distribution to clinical trial centres (Milestone 2).
2. Assess the impact of OPN-301 on graft rejection using pre-clinical allograft mouse models of renal & cardiac transplantation (Milestone 3).
3. Undertake additional in vitro and in vivo studies to identify TLR2 endogenous ligands which result from I/R damage post renal transplantation to further understand the drivers of DGF. (Milestone 4).

4. Undertake additional in vitro and in vivo studies to identify a novel biomarker for kidney damage (Milestone 5). Determine surrogate markers of kidney function and damage applicable for the clinical trial studies and mechanism of action of OPN-305.
5. Secure regulatory approval to conduct the clinical trials, recruit individuals and execute the proposed clinical studies, Phase I (Milestone 6) and Phase II (Milestone 7).

OPN-305

OPN-305 is a fully humanised monoclonal antibody that specifically recognises Toll-like Receptor 2 (TLR2). OPN-305 is derived from the murine parent monoclonal antibody OPN-301 and is an antagonistic antibody which has been shown to block TLR-2 signaling.

OPN-305 is under development by Opsona Therapeutics as a novel treatment for the management of inflammatory conditions driven by inappropriate or excessive activation of innate immune pathways. The initial clinical indication for OPN-305 is the prevention of Delayed Graft Function following renal transplantation in patients at high risk of this complication.

Function of TLR2

There are currently 10 (ten) Toll-like receptors described in humans. TLR2 is primarily expressed on cells with a clear role in innate immune responses, including neutrophils, macrophages, and other leucocytes and the vital role of TLR2 in the innate resistance and initiation of adaptive immune responses to infectious agents has been clearly established. Activation of TLR2 (which exists as a complex with TLR1, TLR6 or TLR10) results in release of many pro-inflammatory cytokines. TLR2 expression has been confirmed in several non-pathogen associated inflammatory conditions such as solid organ ischaemia, atherosclerosis, rheumatoid arthritis, Type 1 and 2 diabetes mellitus and lupus erythematosus. Activation of TLR2 by endogenous ligands is thought to be a major contributor to pathology in these conditions.

Of particular interest is the finding that TLR2-mediated immune responses are implicated in ischaemia/ reperfusion damage.

As transplanted organs are subjected to an ischaemic event and subsequent reperfusion insult, it is reasonable to predict that the blockade of TLR2 would reduce organ dysfunction and graft rejection by inhibiting pro-inflammatory cytokine production and cellular influx into the transplanted organ. Another anticipated benefit of treatment to block TLR2 is the lessening of tissue fibrosis as a result of reduced early graft inflammation.

There is now a considerable body of scientific evidence to suggest that TLR2 plays a vital role in transplantation tolerance.

Project Baseline

WP1: Non Clinical Studies

Preclinical toxicology studies were performed in work package 1, WP1. These studies were performed in cynomolgus monkey and in CD-1 mice by Huntingdon Life Sciences (HLS). Pivotal toxicity studies of four weeks were performed in order to enable entry of OPN-305 in to

Phase I/II trials in humans. EU Funds to support the pivotal cynomolgus monkey toxicology studies, were used as part of the MABSOT programme.
The elements of the non-clinical toxicology studies as they pertain to MABSOT are as follows:

1) Issue of the mouse pivotal toxicology study report.

2) Pivotal cynomolgus monkey toxicology study

3) Issue of the Pivotal cynomolgus monkey toxicology report.

4) Non-clinical expert report.

WP2: IMP Manufacture
Manufacture of OPN-305 drug substance was undertaken though a sub-contract with Lonza UK and successfully developed and delivered pilot material for initiation of pilot and pivotal toxicological studies. Following on from these activities the MABSOT project has developed the Investigational Medicinal Product (IMP), also known as the Drug Product, manufacturing process required for the OPN-305 clinical trial material. IMP manufacture refers to finished product, active (OPN-305) and placebo materials. IMP manufacture is being performed by Patheon UK Ltd, Kingfisher Drive,Covingham,Swindon,Wilshire SN3 5BZ UK. Funds to support the IMP manufacture (fill finish) only were used as part of the MABSOT project.

WP3: In vivo efficacy studies of OPN-301 in murine models of acute and chronic rejection.
In terms of pharmacology, relevant animal model studies of organ-specific I/R injury have been investigated and have established further "proof of concept" for use of OPN-305 in the prevention of I/R injury in solid organs (e.g. mouse renal transplant models). The MABSOT project will further these pre-clinical studies establishing the feasibility of OPN-305 in other organ transplant settings by examining the therapeutic potential of OPN-301 (parent murine antibody of OPN-305 which shares 100% homology in its antigen (TLR2) binding regions with OPN-305) in acute and chronic rejection in a mouse cardiac transplant model. OPN-305 cannot be used in these studies as the rejection studies are performed over a 3-4 month period and as such a mouse anti-human antibody response may be mounted against the OPN-305 protein. In order to avoid this risk, we have therefore chosen to use the murine parent OPN-301, which has been shown to be equivalent in potency to OPN-305 for both human and mouse TLR2. Furthermore, using a mouse model, we aim to determine the impact of OPN-301 in the development of chronic graft rejection in renal transplantation which is the primary clinical indication for OPN-305. These studies will provide valuable insights into the longer term impacts of TLR2 blockade on graft survival rates.

WP4: Identification of endogenous TLR2 ligands associated with TLR2-mediated ischaemia-reperfusion injury
As previously discussed signalling through TLR2 is now believed to play a vital role in the inflammation and tissue damage associated with organ reperfusion. A number of putative TLR2 ligands which drive TLR2-mediated inflammatory responses, such as serum amyloid A and high mobility group box-1 protein, have been identified but to date no correlation between an increase in these or other proteins and tissue damage has been examined. The MABSOT project represents the first scientific study which will attempt to identify the key TLR2 ligands involved

in transplant inflammation and to correlate these proteins to the level of tissue damage expanding the scientific understanding of the inflammatory processes associated with solid organ transplantation.

WP5: Identification of Biomarkers for Kidney Damage and DGF

In addition, the MABSOT project using a combination of protein ELISA (Enzyme-Linked Immuno-sorbent Assay) and gene microarrays techniques will attempt to identify a new clinically relevant marker of early kidney damage. Currently, clinical assessment of kidney failure and kidney damage is difficult because the biomarkers available to clinicians cannot differentiate between causes of kidney failure. The biomarker most frequently used is the serum creatinine value. However, this marker is not an early marker of kidney damage. By the time serum creatinine levels are elevated more than 50% of kidney function has been lost. Another clinically applied estimation of kidney function is urinary creatinine clearance that reflects glomerular function. Renal I/R injury primarily causes tubular damage followed by secondary loss of glomerular function. Therefore, the ideal biomarker of I/R injury would increase early after the injury and be a specific measure of tubular injury. As such there is an urgent need to identify a novel, effective and sensitive biomarker for acute ischaemic kidney damage so that appropriate therapy can be started. A robust biomarker requires a degree of longevity in signal consequently the 6hr time point used to assess gene alterations represents a meaningful duration post-surgery but is still significantly in advance of the creatinine measure which is normally observed at 24 hours. We will therefore seek to identify gene changes that occur at 6 hours and correlate these to known changes in creatinine at 24 hours which will serve as an important anchor point and performance indicator for the study.

WP6: OPN-305 Clinical Trials PhaseI/II

Ultimately the primary objective of MABSOT is to establish OPN-305 as an effective specific treatment to prevent DGF post organ transplantation. Phase I trials will establish the dosing parameters, pharmacokinetics and safety profile of OPN-305 in healthy human subjects. In Phase II clinical trials, as there is currently no specific treatment for DGF, OPN-305 represents a 'first in class' drug. The prevention of DGF post solid organ transplantation has been selected as the clinical indication based on Opsona's previous pre-clinical data demonstrating that blockade of TLR2 by OPN-305 prevents ischaemia/reperfusion injury in murine and porcine cardiac I/R models and in murine renal transplantation models.

3. MAIN S/T RESULTS/FOREGROUNDS

Work Package 1 (WP1): Non Clinical Studies

Description of Work

Non-clinical (toxicology) studies were performed at the Huntingdon Research Centre, Woolley Road, Alconbury, Huntingdon, Cambridgeshire, PE28 4HS, UK. The programme was designed to support First in Human (FIH) studies in healthy volunteers and in patients for short term acute indications, including the lead renal ischaemia/reperfusion indication, and to support single doses or short term exposures up to 2 weeks duration. Based on preclinical data for OPN-305, mouse and cynomolgus monkey were selected as the toxicology species.

Pilot toxicity studies were initiated in June 2010 and were completed in August 2010.

Pivotal Toxicity studies were initiated in September 2010 and in life studies were completed in late December 2010.

The elements of the non-clinical studies as they pertain to MABSOT were as follows:

1) Issue of the mouse pivotal toxicology study report.
2) Pivotal cynomolgus monkey toxicology study
3) Issue of the Pivotal cynomolgus monkey toxicology report.
4) Non-clinical expert report.

Results

All studies associated with WP1 are now complete. WP1 has now been successfully concluded.

Pivotal GLP (Good Laboratory Practice) toxicity studies of four weeks duration were conducted in monkeys, with dosing once weekly at dosages up to 100 mg/kg/week. No signs of overt toxicity were observed at dosages up to 100 mg/kg/week, with no effects on in-life parameters, including clinical pathology investigations, and no treatment-related histopathological changes were observed. Toxicokinetic data demonstrated increasing exposure with increasing dose, with some degree of accumulation after four weekly administrations of OPN-305. There was 100 % saturation of TLR2 binding sites on monocytes in the monkey toxicity study at all dosage levels (10, 30 and 100 mg/kg/week) at completion of the dosing and recovery periods. Immune function testing conducted in the toxicity studies revealed no effects of OPN-305 on lymphocyte populations in both species up to 100 mg/kg/week, and no effect on primary T-cell mediated antibody responses in monkeys at any dosage.

The no-observed-adverse-effect- level (NOAEL) in the four week toxicity studies in mice and cynomolgus monkeys was 100 mg/kg/week in both species.

Safety pharmacology end-points were examined in monkeys, with no effects of OPN-305 on ECG (including QT interval), blood pressure, body temperature, neurobehavioural assessments or respiration rate. No evidence of irritation at intravenous injection sites was observed in monkeys, and an *in vitro* haemocompatability study showed no haemolytic potential of the OPN-305 formulation in human, mouse or monkey blood.

Tissue cross reactivity data indicated that OPN-305 binds principally to leucocytes in the blood, bone marrow and lymphoid organs, with some binding also possible in epithelial tissues and smooth muscle. Although some evidence of binding of OPN-305 to ocular and testicular tissues was observed in the tissue cross reactivity study, it is unlikely that OPN-305 will penetrate these sites to any significant degree after *in vivo* administration, in view of blood-eye and blood-testis barriers being relatively impermeable to large molecules such as antibodies. Therefore, in conclusion, the OPN-305 binding observed in the cross reactivity study in human tissues was consistent with the expression of TLR2 reported in the literature, and there was no evidence of unexpected or 'off-target' (cross-reactive) binding in this study.

In conclusion OPN-305 was well tolerated in the monkey pivotal toxicology studies. Based on the results of the preclinical toxicity studies, there is no acute concern about the safety of OPN-305 in humans.

All Deliverables (1.1-1.4) for WP1 have been submitted within the first reporting period. Submission of all deliverables also constitutes completion of milestone 1 (MS1) associated with WP1.

WP2: IMP Manufacture

Description of Work

IMP manufacture refers to finished product, active and placebo materials. IMP (Drug Product) manufacture has been performed by Patheon UK Ltd, Kingfisher Drive, Covingham, Swindon, Wilshire, SN3 5BZ UK. Funds to support the IMP manufacture (fill finish) only are being sought as part of this WP.

Once completed the IBIMP (Drug Substance) batch was transferred for IMP manufacture and aseptic sterilization in preparation for the clinical trial activities. 1000 vials of active drug product (OPN-305) and placebo have now been manufactured by Patheon. Stability studies on this material are ongoing.

Results

First reporting period (Dec01 2010-May 31 2012).

The fill finish process is divided into 2 distinct activities, feasibility testing and clinical trial batch manufacture. Feasibility manufacture commenced in August 2010 and analysis of this batch and subsequent report was concluded in November 2010. OPN-305 is the lead development compound of Opsona Therapeutics and the company is committed to the clinical development into Phase II trials with this compound. As such the various development activities, manufacture, toxicology etc were activities planned to commence irrespective of whether EU funding could be secured to support these activities.

Based on Opsona's independent development timelines for OPN-305 analysis of the feasibility batch manufacture of the IMP material was planned to commence in September 2010. It was anticipated that this activity would coincide with the start date of the MABSOT programme; as such Deliverables 2.1 through 2.3 in WP2 were designated to this activity.

Feasibility batch manufacture (Deliverable 2.1) commenced as scheduled in August 2010, analytical testing on this batch (Deliverable 2.2) concluded in September 2010 and the resulting development report (Deliverable D2.3) was issued in November 2010 prior to the official start date (December 1st 2010) of the MABSOT programme, as a result of protracted MABSOT contract negotiations.

The manufacture of the laboratory (feasibility) batches of OPN-305 10mg/ml solution and placebo solution were successfully completed (Deliverables 2.1-2.3).

Active Substance Batch Manufacture

Three OPN-305 IMP batches have been produced to date: Clinical batches PD10209 and PD11245, both derived from IBIMP GMP batch 10P20017, and batch PD10139, derived from the IBIMP pilot batch P420244 and filled under non-GMP conditions.

The batch size of the GMP OPN-305 IMP batch PD10209 (used in the Phase I clinical trial) was approximately 1000 x 5 mL (nominal fill size). The batch size of GMP OPN-305 IMP batch PD11245 (to be used in the Phase II clinical trial) was approximately 5000 x 5 mL (nominal fill size).

OPN-305 IMP is formulated in 25 mM sodium citrate / 125 mM sodium chloride / 6 mM citric acid 0.01% (w/v) Polysorbate 20, pH 5.5. The formulation of the IMP is the **same as** the formulation of the IBIMP.

Two GMP batches of the OPN-305 IMP have been manufactured to date by Patheon Ltd. (Swindon, UK). For manufacture of the Phase I & Phase II clinical material, the OPN-305 IBIMP batch, 10P20017, was used. GMP production of the Phase I clinical batch PD10209 was performed in January 2011 and Phase II batch PD11245 in December 2011. One batch (PD10139) derived from the pilot IBIMP batch P420244, was filled under non-GMP conditions in August 2010; this batch is used for stability testing. An additional IMP fill was also performed in 2014, however as a results of microbiological contamination additional testing was required by Lonza in order to release this batch for clinical use.

Placebo Batch Manufacture

Three batches of placebo IMP have been manufactured; 1 pilot batch and 2 GMP batches. The batch size of pilot OPN-305 Placebo batch PD10138 was 932 x 5 mL (nominal fill size).

The size of the first GMP OPN-305 Placebo batch PD10210 was approximately 1000 x 5 mL (nominal fill size) while the size of the second clinical batch PD11244 was approximately 15,000 x 5 mL (nominal fill size).

The components of Placebo bulk solution are sodium chloride, sodium citrate, citric acid, Polysorbate 20 and water for injection.

Two GMP batches of the Placebo IMP have been manufactured to date by Patheon Ltd, Swindon, UK. For manufacture of the Phase I clinical supply, the OPN-305 Placebo batch PD10210 was manufactured in January 2011 and batch PD11244 for the Phase II trials was manufactured in December 2011. One batch (PD10138) was filled under non-GMP conditions in August 2010; this batch is used for stability testing.

The specification of the IMP material (active and Placebo) for both Phase I and Phase II material were described in further detail in submitted Deliverable, D2.4 (May 24 2012).

Deliverables 2.1-2.4 inclusive were submitted during the first reporting period.

2nd reporting period (June 01 2013-May 31 2014).

Deliverable 2.5: Executed batch records for IMP

IMP (Drug Product) manufacture refers to finished product, active and placebo materials. IMP manufacture was performed by Patheon UK Ltd, Kingfisher Drive, Covingham, Swindon, Wilshire SN3 5BZ UK. Funds to support the IMP manufacture (fill finish) only are being sought as part of this WP. Once manufacture of the IBIMP (Drug Substance) was completed at Lonza, UK it was transferred to Patheon for IMP manufacture and aseptic sterilization in preparation for the clinical trial activities. IMP, Active drug product (OPN305) and placebo, were manufactured

by Patheon for both Phase I and Phase II clinical trials. Submitted Deliverable 2.5 provided the executed batch records for the IMP material (active and placebo) for both Phase I and II

Deliverable 2.6: QP Certification

Once the OPN-305 IMP was manufactured and released it was shipped to Almac Clinical Services (Craigavon, UK), for QP release, labelling, storage and distribution to clinical sites. The QP release of (OPN-305 10mg/ml solution) and placebo IMP were successfully completed by Almac Clinical Services ahead of both Phase I and Phase II Clinical Trials. No issues were identified.

Submitted Deliverable 2.6 provided the qualified person (QP) release certificates for both active (OPN-305 10mg/ml sterile solution) and placebo IMP for both Phase I and Phase II trials.

Deliverable 2.7: CMC documentation for IMPD

An IMPD (Investigational Medicinal Product Dossier) is a compilation of quality, non-clinical and clinical data on the investigational product to be evaluated in a clinical trial and is submitted at the time of clinical trial application.

Submitted Deliverable 2.7 detailed the Chemistry Manufacturing Control (CMC) or Quality section of the IMPD (Version 4, July 9th 2012) for OPN-305 (both Phase I and Phase II material).

WP3: In vivo efficacy studies of OPN-301 in murine models of acute and chronic rejection.

Description of Work

Objective 1: the effect of OPN-301-mediated TLR2 inhibition on the development of chronic allograft lesions in a murine model of heart allo-transplantation.

Objective 2: the effect of OPN-301 on acute cardiac allograft rejection by the innate and adaptive immune system in a murine model of heart transplantation treated with OPN-301

Objective 3: the effect of OPN-301 on chronic renal allograft rejection by the innate and adaptive immune system in a murine model with OPN-301

OVERALL SUMMARY OF WP3 RESULTS

D3.1: Chronic Cardiac Rejection model

OPN-301 has been tested in mouse model of chronic cardiac rejection at 1mg/kg. No therapeutic effect was observed.

D3.2: Acute Cardiac Rejection model:

Overall, treatment with OPN-301 did prolong allograft survival. However this prolongation was modest, with a difference in mean survival time (MST) of three days. Many other treatment protocols in similar models of mouse heart transplantation result in indefinite graft survival, i.e. a difference in MST of >100 days. This observation is not surprising, as rejection of fully allogeneic heart grafts is multi-factorial and blockade of one pathway, in this case, TLR2 is unlikely to eliminate rejection completely

D3.3: Chronic Renal Rejection model:

On investigation in a murine model of chronic renal rejection of the effect of administration OPN-301, compared with administration of the isotype control on inflammatory processes, it was found that OPN-301 also significantly improved allograft kidney function, as determined by measuring blood urea nitrogen in the mice. The results indicate that repeated administration of anti-TLR2 MAb may have beneficial effects in improving renal function post-transplant and thus potentially reducing chronic renal rejection in a clinical setting.

WP3 was successfully completed and all deliverables associated with this work package were submitted to the Commission in the second reporting period.

WP4: Identification of endogenous TLR2 ligands associated with TLR2-mediated ischaemia-reperfusion injury

Description of Work

It is highly likely that endogenous ligands that activate innate immune pathways are released during the ischaemic periods associated with transplant. Identifying this ligand, or most likely ligands, would be useful in the identification of a biomarker or potentially an as alternative treatment target.

Objectives:

- Identify the TLR2 ligands which are induced/generated as a result of I/R injury.
- To test the in vitro efficacy of these ligands and their ability to be blocked by OPN-305.
- To confirm the presence of these ligands in a specific mouse genetic knockout model & in the clinical setting.

Results

First reporting period (Dec01 2010-May 31 2012)

A brief summary of the results from the first reporting period (submitted Deliverables 4.1 and 4.2) is provided below. For a full description of the results from the first reporting period, see submitted deliverables D4.1, D4.2 and the first periodic report.

D4.1: Identify the presence of TLR2 endogenous ligands in murine transplant tissue
Submitted Nov. 30 2011.

- Serum from mice sacrificed 6 hours post-transplant, 24 hours post-transplant and sham operated mice were analysed for putative TLR2 ligands. No-pathogen derived putative TLR2 ligands examined included Biglycan, high-molecular weight group box protein -1, heat shock protein70 and Serum amyloid A (SAA). Pathogen (gram + bacteria) derived ligands included Lipoteichoic acid (LTA) and peptidoglycan. Up-regulation of these ligands has been reported in kidney tissue following ischaemia, however, in the murine serum samples obtained from KCL (MABSOT partner#2) only upregulation of SAA was detected post transplantation.

D4.2: Determine whether OPN-305 blocks the activity of these ligands
Submitted Jan. 20 2012.

- SAA shown to activate the THP1 CD14 blue reporter cell line, human monocytic cell line U937, murine macrophage cell line J774 and human primary whole blood cells in a dose dependent and TLR2-dependent manner.

SAA therefore selected as the candidate endogenous TLR2 ligand associated with I/R injury.

Second reporting period (June 01 2012-May 31 2014)

Deliverable 4.4: Using histology of mouse renal tissue determine if TLR2 ligands can be correlated to tissue damage.

Following kidney transplantation it was evident that SAA levels were massively up regulated (over 700 fold). The up-regulation of SAA peaked at 6 hours post-transplant whereas it is apparent that renal damage progressed out to 24 hours. It was therefore difficult to interpret whether SAA levels correlated with the levels of renal damage as the amount of SAA present at 6 and 24 hours was not statistically different whereas histology scoring at 6 and 24 hours was statistically significant (p value <0.0001; unpaired T test). SAA levels were also tested in serum from animals sacrificed 1 hour after transplantation however the SAA levels were undetectable, similar to that observed for the sham controls. BUN levels in these experiments were not statistically different between any of the time points examined in these experiments as these transplant experiments involved removal of a single kidney so the remaining kidney could function to clear BUN from the blood.

Final reporting period (June 01 2014-Sept 30 2014)

Deliverable 4.3: Use of a specific genetic ligand knockout mouse to confirm role in I/R damage

The specific objective of *Deliverable 4.3* was to validate serum amyloid A (SAA) as TLR2-ligand involved in mediating ischaemia reperfusion injury following renal transplantation. The results from *Deliverable 4.1* showed that SAA was the only endogenous TLR2 ligand investigated that showed differential expression in murine transplant serum compared to sham operated control serum. SAA levels showed massive up-regulation both at 6hr and 24 hrs post-transplant compared to the sham operated control animals. The bioactivity of SAA was investigated *in vitro* using purified recombinant SAA in a number of human and murine cell lines as well as in whole blood and it was shown to activate cells in a TLR2 dependent manner (*Deliverable 4.2*). Previously, we have used Blood Urea Nitrogen (BUN) as a readout of renal function when assessing the efficacy of OPN-301 in a murine model of kidney transplantation. The serum BUN concentration correlated with histology and as such is a marker for renal damage. However, in this deliverable we reported that SAA did not appear to play a role in kidney ischaemia reperfusion injury. Renal function as measured by BUN was measured in the serum of wild type or SAA knockout mice (KO) post renal transplant, no difference in BUN levels was observed between the two experimental groups indicating that in the context of renal transplantation SAA is not a critical factor in mediating I/R injury following kidney transplantation.

Deliverable 4.5: Confirm role of these ligands in human I/R responses is associated with transplantation

In the mouse studies performed in WP4 it was observed that serum amyloid A was massively up-regulated (approximately 700 fold) in murine transplant serum vs sham operated control serum (*Deliverable 4.1*) and that recombinant serum amyloid A is able to activate multiple cell lines in a dose dependent manner that is reliant on TLR2 (*Deliverable 4.2*). In addition, in *Deliverable 4.4* SAA it was observed that an increase in SAA levels in the serum of transplant mice may correlate with a decrease in renal function as measured by blood urea nitrogen concentration and kidney histology scores. In the OPN305-102 clinical trial SAA was measured in the serum of renal transplant patients at five time points, at the beginning of placebo or OPN-305 infusion, 1hr, 7hr, 24hr and 48hr post infusion. Correlating with the observations in mouse transplant tissue SAA levels were observed to significantly increase over time. This increase over time following renal transplant is consistent with the known properties of SAA as an acute phase protein which is upregulation in response to tissue damage and inflammation

In the placebo group of patients the levels of SAA were observed to be higher in patients with DGF compared to those without DGF, however due to the large standard deviation in the SAA values between patients this difference was not observed to be statistically significant. Furthermore these apparent differences were only observed at the 48hr time point.

The overall results of the OPN305-102 clinical trial Part A did not show any significant difference between DGF in placebo compared to OPN-305 overall treatment groups. However, a subset analysis appears to demonstrate that treatment with 0.5 mg/kg OPN-305 has a lower DGF rate than placebo for ECD patients. Based on these findings it was decided to examine whether SAA levels in ECD patients displayed a similar trend. In the current study SAA levels in ECD patients with DGF were observed to be lower in patients treated with 0.5mg/kg OPN-305 compared to placebo, whilst no observable difference was noted between placebo and the two higher dose of OPN-305. However, as the numbers of patients within DGF groups is small and variability in SAA levels between patients is high the observed differences in SAA levels are not considered statistically significant
The results of the SAA determinations in human renal transplant serum samples would indicate the following

1) Similar to mouse transplants SAA levels increase significantly in human serum post kidney transplant.
2) A trend was observed showing higher SAA levels in placebo patients at the 48hr time point with DGF compared to non-DGF patients suggesting that SAA may be a biomarker for kidney damage.
3) At the 48hr time point renal transplant patients with DGF treated with OPN-305 at 0.5mg/kg are observed to have lower SAA levels compared to matched placebo patients. This observation was, not noted in patients that did not have DGF.

On an observational level the results would suggest a role for SAA in mediating DGF and that this response may be ameliorated by blocking TLR2. However, as the standard deviation of the

SAA values is large between groups of patients these differences are not considered significant; as such it is not possible to attribute any definitive role for SAA in DGF.

WP5 Identification of Biomarkers for Kidney Damage and DGF

Description of Work

To screen for a novel biomarker of early ischaemic kidney damage using a murine renal iso-graft model. Kidney tissue and serum will be screened with a focus on biomarkers found in serum that is found to correlate with renal tubular damage. The use of this biomarker will then be validated in samples obtained from human transplant patients. Mouse samples will be provided from the transplant experiments conducted at KCL. Human samples will be provided by KCL for the validation studies ahead of the Phase II trial and from all partners during the Phase II OPN-305 clinical trial.

Results

First reporting period (Dec01 2010-May 31 2012)

N/A

Second reporting period (June 01 2012-May 31 2014)

Deliverable 5.1 Screening known renal biomarkers/inflammatory factors to establish a correlate with renal damage.

The specific objective of Deliverable 5.1 was to screen known renal biomarkers/inflammatory factors to establish a correlate with renal damage. As well as validating known biomarkers/inflammatory factors this deliverable also served as a risk mitigation activity in the event that no suitable novel candidates were identified in D5.2-D5.4.

The following reported biomarkers/inflammatory factors were screened in this study:

- NGAL (Neutrophil Gelatinase Associated Lipocalin)
- KIM1 (Kidney Injury Molecule-1)
- Cystatin C
- KC (Keratinocyte derived protein Chemokine)

Serum samples from animals sacrificed 1 hour, 6 hours, 24 hours and 48 hours post kidney transplantation were analysed for the molecules above as well as serum from sham operated animals. Kidney damage scoring was assessed by histology scoring.

The results showed that no difference was observed between levels of NGAL, KIM1 and Cystatin C in the serum from mice that have undergone a kidney transplant. However, KC levels plotted alongside renal damage scores showed that renal damage peaked at 24 hours whereas KC levels peak at 6 hours. Although a definitive correlate between renal damage and KC levels was not established the results may indicate that an early and significant increase in KC levels may be

an indicator of kidney damage which only becomes apparent subsequently (either through kidney function or histologically). As such KC maybe a useful predictive tool for kidneys with moderate to severe damage.

Deliverable 5.2: Identification of 50-200 genes differentially regulated in murine kidney transplantation

Two rounds of transplant experiments have been performed in WP5, the first round of transplant experiments were performed in D5.2 and provided material for the microarray experiments and the second, material for the qPCR validation experiments (D5.3) for gene hits identified in the microarray experiments.

Based on analysis of variance (ANOVA):

- 1,819 probe sets were identified with variable expression across the three time points.
- 438 differentially expressed probe sets have been identified between **sham operated** and **6 hours post-transplant** samples.
- 306 differentially expressed probe sets were identified between **sham operated** and **24 hours post-transplant** samples.
- 31 differentially expressed probe sets were identified between **6 hours post-transplant** and **24 hours post-transplant** samples.

- Hierarchical clustering analysis of the 1819 probe sets with variable expression across the time points revealed gene expression similarities between the 2 transplant time points (6hr and 24hr).

Following discussions between Opsona, Prof. Steven Sacks KCL and Almac it was decided that a further analysis of the microarray data should be performed. Specifically, it was agreed that an unbiased analysis should be performed in order to identify genes with high up-regulation at 6hrs irrespective of any known database association with I/R injury.

A summary of the additional analysis is provided below:

A. Unbiased analysis was conducted to identify genes highly upregulated at the 6 hour time point compared to the sham treated samples. In this analysis, no filter was applied to identify targets with secreted protein products.

B. The genes to be considered as potential biomarkers were selected based on:

i. Evaluation of the robustness of expression change (genes with significant variable expression across time points and significantly up-regulated between 6 hours post-transplant and sham operated)

ii. Presence of human orthologs

iii. Relationships with relevant functional processes (I/R injury) were established but not used for filtering the genes in order to maintain an unbiased approach.

Following completion of the analysis, 251 probe sets mapping to 209 genes which passed the selection criteria were identified and ranked by decreasing fold change. Twenty of the probe sets in the results were previously identified as potential candidate biomarkers using additional criteria such as relevant functional processes and marker location.

Following review of the results from this second analysis by Opsona and KCL, a final list of 20 targets was generated. These 20 gene hits were taken forward for qPCR assessment in the independent mouse samples as detailed in the description of work for WP5. The results of these gene expression validation studies were reported in Deliverable 5.3 (below).

Deliverable 5.3: Generate prioritised list of genes based on correlation with histology & presence of human ortholog.

The specific objective of *Deliverable 5.3* was to generate a prioritized list of genes from the mouse microarray data generated by Almac and take these forward and investigate in human transplant samples for differential expression.

As previously stated main objective of this study was to facilitate the selection of candidate biomarker of potential early biomarkers of renal damage by combining results from microarray and qPCR experiments. For 16 out of 20 genes identified in D5.2, gene expression assessed by qPCR analysis of independent samples validated the microarray study used to select these potential targets based on their significant up-regulation between 6 hours post-transplant and sham operated. Following, a further filtering process and correlating qPCR and protein levels of the candidate biomarkers in mouse transplant serum samples, two gene target, SPP1 (Osteopontin) and Tissue Inhibitor of Metalloproteinase-1 (TIMP-1), were selected for further analysis and validation in the human phase II clinical trial.

Final reporting period (June 01 2014-Sept 30 2014)

Deliverable 5.4: Confirm gene hits in small sample of human transplant blood samples and validate gene hits in PII trials.

Deliverable 5.4 was split into 2 separate components:

1. Pilot study: Confirmation in a small number of human transplant samples independent of the OPN-305 Phase II trial
2. Validation of the biomarkers in the transplant samples obtained in the OPN-305 Phase II clinical trial as described in WP6.

The main objective of Work Package 5 was to facilitate the selection of candidate early biomarkers of renal damage by combining results from microarray and qPCR experiments. In Deliverables 5.2 and 5.3 following a filtering process and correlating qPCR and protein levels of candidate biomarkers in mouse transplant serum samples, two gene targets, SPP1 (Osteopontin)

and TIMP-1, were selected for further analysis and validation in the human patient samples. In the mouse experiments RNA levels of SPP-1 and TIMP-1 were observed to be significantly upregulated in whole blood cells 6hr after renal transplant (*Deliverable 5.3*), serum protein levels of both biomarkers were also upregulated (*Deliverable 5.3*) 6hr after renal transplant.
In the pilot study serum samples from patients enrolled in the KALIBRE study at KCL, patients were split into 2 groups, DGF patients, defined as the need for dialysis within 7 days post-transplant and non-DGF patients. Serum samples were tested by ELISA for protein levels of the biomarkers at the time of surgery, 6hr and 24hr post-transplant. Similar to the results in the mouse studies in D5.3 levels of SPP-1 were observed to increase over time post-transplant, the kinetics of TIMP-1 secretion was observed to be more variable with increases observed in some patients and not in others. However, no significant difference between patients with DGF and non-DGF in the kinetics or serum concentrations of SPP-1 or TIMP-1 was observed.

In the OPN305-102 clinical trial SPP-1 and TIMP-1 RNA levels were measured in whole blood cells of renal transplant patients at five time points, at the beginning of placebo or OPN-305 infusion (t=0), 1hr, 7hr, 24hr and 48hr post infusion. Similar to the mouse experiments the levels of SPP-1 RNA were observed to increase at the early time points of 1hr and 7hr post infusion, increasing Cq values thereafter indicated that the level of SPP-1 expression, relative to the reference gene, was returning to pre-transplant levels. Negative Cq values were obtained for TIMP-1 at all-time points indicating that expression of this biomarker was increased at all-time points relative to the reference genes.

SPP-1 (Osteopontin) and TIMP-1 have been reported to be important predictors of acute renal rejection (Wang et al 2013, Jin et al 2013, Mazanowska et al 2011, Mazanowska et al 2013).
Early renal rejection usually occurs within the first 3 months after transplant; however, the objective of this study was to establish whether either SPP-1 or TIMP-1 could be validated as early biomarkers of renal damage. Clinical assessment of kidney failure and kidney damage is difficult because the biomarkers available to clinicians cannot differentiate between causes of kidney failure. The biomarker most frequently used is the serum creatinine value. However, this marker is not an early marker of kidney damage. By the time serum creatinine levels are elevated more than 50% of kidney function has been lost. Another clinically applied estimation of kidney function is urinary creatinine clearance that reflects glomerular function. Renal I/R injury primarily causes tubular damage followed by secondary loss of glomerular function. Therefore, the ideal biomarker of I/R injury would increase early after the injury and be a specific measure of tubular injury. There is an urgent need to identify a novel, effective and sensitive biomarker for acute ischaemic kidney damage so that appropriate therapy can be started early.

The results from the assessment of RNA expression of SPP-1 and TIMP-1 in whole blood cells of renal transplant patients from the OPN305-102 clinical trial suggest that SPP-1 may be an early biomarker for tubular injury as SPP-1 RNA levels were observed to increase significantly 1hr and 7hr post infusion in placebo as well as OPN-305 treatment groups. However, no differences in the RNA expression of SPP-1 at the early time points is observed between DGF and non-DGF patients, results were somewhat more variable when the different patient subsets, ECD, DCD and SCD were analysed but in general there is no difference between SPP-1 levels in DGF and non-DGF patients in the patient subgroups. In addition, OPN-305 was not observed to influence the expression of SPP-1 at any of the doses tested.

In conclusion the results of Deliverable 5.4 indicate:

1) SPP-1 RNA levels significantly upregulate shortly after transplant.

    - This upregulation is transient and does not appear to correlate with renal function as measured by DGF, as evidenced by the same observation in placebo, suggesting that the increase in SPP-1 may be a more general marker for inflammation, perhaps related to the transplant procedure itself.

2) Inhibition of TLR2 does not impact SPP-1 expression.

3) Although TIMP-1 levels were observed to be higher relative to the reference genes at all the time points tested, no differential expression of TIMP-1 was observed indicating this molecule does not influence early renal function post-transplant.

    a. Inhibition of TLR2 does not affect TIMP-1 expression

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WP6: OPN-305 Clinical Trials Phase I/II

Description of Work

Phase I Healthy Volunteer Study

A single centre, prospective, randomised, double-blind, placebo controlled, sequential, dose-escalating phase I study to assess the safety and tolerability of intravenously infused single doses of OPN-305 in healthy subjects.

Phase II Study

A Three-Part, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Sequential Adaptive, Phase II Study to Evaluate the Safety, Tolerability and Efficacy of OPN305, a Humanised Monoclonal Antibody that Blocks Toll-Like Receptor 2, in Renal Transplant Patients at High Risk of Developing Delayed Graft Function

1. Phase 0: to assess OPN-305 dose in renal transplant patients, commenced and concluded Q4 2012.
2. Part A: first part of the double blind study commenced in April 2013 in 144 renal transplant patients. Patient enrolment concluded in April 2014 with recruitment of 139 patients fulfilling the criteria of 34 eligible patients per group
3. Part B: In progress

Results

Phase I: Study Protocol# OPN-305-101

A Phase 1 study to assess the safety and tolerability of a single intravenous infused dose of OPN-305 in healthy subjects commenced June 30 2011, database lock was in February 2012 and the final Phase I study report was issued in June 2012.

The primary objectives of the study were i) to assess the safety and tolerability of single ascending intravenously infused doses of OPN-305 in healthy subjects and ii) to determine the dose and infusion time for Phase II/III programme. Secondary objectives were i) to determine the pharmacokinetic profile of OPN-305 after a single intravenous infusion in healthy subjects, ii) determine the immunogenicity of OPN-305 after a single intravenous infusion in healthy subjects, iii) confirm that there are no unexpected (clinically meaningful) elevations of cytokine levels in serum (e.g. TNFα, IL-1β, IL-6 and IFN-γ) following a single intravenous (iv) dose of OPN-305, and iv) to evaluate the effect of OPN-305 on PD parameters (total white blood cell count, ex vivo whole blood assay and target occupancy (TLR2 saturation on monocytes)).

Subjects were male healthy subjects, 18 to 60 years of age and in good health as determined by past medical history, physical examination, vital signs, 12-lead ECG, and laboratory tests at screening. Six cohorts, of between 6 and 8 subjects per cohort, were dosed and followed for 90 days post dose. Doses ranged between 0.5 mg/kg and 10 mg/kg.
The compound was very well tolerated with few adverse events (42 Treatment emergent adverse events (TEAE)'s in 24 subjects, from a total of 41 (29 active and 13 placebo) subjects treated, mainly mild headache, dizziness, common cold, and mild GI symptoms, with only 3 mild events in 2 subjects were considered treatment related (headache in placebo and 5 mg/kg OPN-305 and frequent bowel movements in 5 mg/kg OPN-305).

Two subjects had Serious Adverse Events (SAE)'s reported, both of whom received placebo; these were of a cerebrovascular accident and cruciate ligament rupture.

There have been no vital sign, ECG, haematology, clinical chemistry or urinalysis findings of any clinical significance (as defined by the principal investigator). No effects on endogenous cytokines were observed.

Pharmacokinetic and pharmacodynamic data have demonstrated the following:

- Receptor occupancy has been demonstrated, at levels of up to 100% in subjects at all doses.
- Duration of 100% receptor occupancy has been 7 days or longer at all doses.
- The pharmacokinetics of OPN-305 is dose proportional including the half-life.
- The whole blood assays also demonstrate that inhibition of IL-6 stimulation has been demonstrated at all doses.

<u>Phase I follow up study</u>

The results of the Phase I study demonstrated that OPN-305 was very well tolerated at doses up to and including 10mg/kg in healthy subjects. Toll-like receptor-2 (TLR-2) occupancy >70% at 90 days post dose was noted in the highest two dose levels (5 mg/kg and 10 mg/kg) in a total of 11 subjects. Additional follow up was considered appropriate for these subjects in order to assess the degree of receptor occupancy at a 7-8 months post the 90 day follow up visit).

All 11 subjects had receptor occupancy levels back to the mean levels noted for placebo in the original study (OPN-305-101) which ranged between 9.6% and 12.5% throughout the study. Therefore no further follow up was considered necessary in these subjects.

Phase II Study (Study Protocol OPN305-102)

Study Title:

A Three-Part, Multi-centre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Sequential Adaptive, Phase II Study to Evaluate the Safety, Tolerability and Efficacy of OPN-305, a Humanised Monoclonal Antibody that Blocks Toll-Like Receptor 2, in Renal Transplant Patients at High Risk of Delayed Graft Function**.**

Study Design: This is a three-part, group sequential, adaptive, Phase II study to assess the safety and to evaluate the clinical effect of single intravenous doses of OPN-305 on renal function in patients scheduled to receive a kidney transplantation from:

- An extended criteria donor (ECD) (subject to a limit of 50% of all patients in Parts A) defined as:
  - Donor ≥60 years of age
  - Donor 50-59 years of age with all three of the following criteria present:
    - Death due to cerebrovascular accident
    - Pre-existing history of systemic hypertension
    - Terminal serum creatinine ≤1.5mg/dL

  OR
- Donation after circulatory death (DCD) - previously "Donation after Cardiac Death" and "Non Heart Beating Donors"

  OR
- A standard criteria donor (SCD) with a cold ischaemic time (CIT) greater than 18 hours at the start of the study-drug administration (SCD[CIT>18h])

Phase 0: Prior to the initiation of the double-blind, randomised study there was an open-label, single arm, pilot (Phase 0) pharmacokinetic/pharmacodynamic (PK/PD) evaluation of single-dose intravenous (IV) dose of OPN-305 1.5mg/kg over 28 days, receptor occupancy (RO) over 14 days and safety over 28 days in 8 patients.
The data generated in Phase 0 were used to select the doses of OPN-305 for Part A of the double-blind, randomised study according to the definition below.

- If adequate RO is achieved, the study will continue with single IV doses of OPN-305 0.25, 0.5 and 1.5mg/kg IV.
- If RO is considered inadequate the two lower doses (0.25 and 0.5mg/kg) will be substituted with the two other doses tested in the Phase I study (*i.e.*, single-dose OPN-305 5 and 10mg/kg IV) and the study will continue with single IV doses of OPN-305 0.5, 1.5 and 5mg/kg **OR** 1.5, 5 and 10mg/kg IV.

The data from Phase 0 for 8 patients dosed with 1.5 mg/kg OPN-305 was reviewed by an independent Data and Safety Monitoring Board (DSMB) who were also tasked to determine the dose range for the dose-finding in Part A of the double-blind part of the study.
The DSMB determined that the safety profile, with no adverse events considered related to OPN-305, was in line with what would be expected from this transplant population. In the 8 patients treated there were 108 events most of which were mild or moderate in intensity. There have been 7 serious adverse events in 5 patients all of which were considered unrelated to OPN-305 consisting of graft (surgical) complications, thrombo-embolic events and bladder infection.
The pharmacokinetic data demonstrated that the AUC was approximately 30% of that seen with the same dose in the Phase I study and in terms of TLR2 receptor occupancy, whilst all patients had near full receptor occupancy at 7 days, two of the eight patients had a reduction to baseline of receptor occupancy at 14 days. Therefore, the DSMB considered that the most appropriate dose range for Part A of the study would be 0.5 mg/kg, 1.5 mg/kg and 5 mg/kg.
The data from patients in Phase 0 will not be used in the main Phase II study.

Part A: This was a single-infusion, dose-confirmation part of the study to determine the optimal IV dose to be studied further in Part B. The rationale was to confirm whether there is a

difference in dose required should receptor upregulation require a higher dose for the same occupancy period and to assess if there is a trend to better efficacy based on the primary endpoint. Three IV doses of OPN-305 were compared to IV placebo and were randomised 1:1:1:1. The planned interim analysis at the end of Part A was completed as planned by the DSMB who assessed safety, and reviewed the PK/PD and efficacy data.

It was planned that 144 patients would be randomised in Part A; 36 patients in each of the 4 dose groups to ensure a minimum of 34 evaluable patients per group. Eventually, 161 patients were screened, 146 randomized and 139 treated with study drug; 34 patients in the placebo group, 34 in the 0.5mg/kg group, 37 in the 1.5mg/kg dose group and 34 in the 5mg/kg group. The donor types for the 139 patients treated were: 68 ECD, 45 DCD and 26 SCD. Receptor occupancy (RO) profiles were generated for all patients and PK profiles were generated for 37 patients (a minimum of 12 patients in each of the 4 dose groups).

In Part A dose-dependent 100% receptor occupancy on circulating monocytes was observed. Upregulation of the TLR2 receptor was confirmed in the disease state. The mean duration of % R.O. increased with increasing dose level from 0.5 to 5.0 mg/kg and was shorter than for equivalent doses in healthy volunteers. The mean duration of 100% R.O. was:

- 1 Day in the 0.5 mg/kg group
- 6 Days in the 1.5 mg/kg group
- 13 Days in the 5.0 mg/kg group

The PK data from Part A showed exposure to OPN-305 increased with increasing dose level. The half-life increased with increasing dose which was also seen in HVs and there was lower systemic exposure at the same dose compared with HVs. The PK data from Part A were similar to those seen in the 8 patients in Phase 0.

Overall, there does not appear to be any apparent difference between patients and HVs in the relationship between serum OPN-305 concentration and blood TLR-2 RO. Serum OPN-305 concentrations <1,000 ng/mL were associated with a trend towards lower receptor occupancy.

Data from 139 patients were reviewed by the DSMB including a total of 41 patients who received dialysis in the first 7 days; adjudication showed 40 cases with DGF and 1 case of hyperkalaemia.

The key efficacy finding was that the DGF rate (defined as the need for dialysis in the 7 days post- transplantation) was unexpectedly low (29%) in the placebo arm. The DGF and functional DGF (fDGF, failure of serum creatinine to decrease by at least 10% daily on 3 successive days during the first week post transplantation) rates observed were:

DGF	**fDGF**
0.5 mg/kg – 26.5%	0.5 mg/kg – 38.2%
1.5 mg/kg – 29.7%	1.5 mg/kg – 51.3%
5.0 mg/kg – 35.3%	5.0 mg/kg – 52.9%
Placebo – 29.4%	Placebo – 52.9%

There were 182 SAEs in 91 Patients as of 30th April 2014 of which 3 patients had SAEs considered related to OPN-305/placebo: CMV pneumonitis (also with sepsis, atypical pneumonia), acute graft failure (with hypercalcaemia) and immediate poor renal perfusion. There were 3 deaths one of which was deemed related to the study drug: CMV pneumonitis and sepsis

(related), CMV pneumonia (unrelated), and haemorrhage from an infected ilio-femoral arterial prosthesis (unrelated). The most frequently reported SAEs were:

- 23 rejection/suspicious biopsy SAEs reported in 22 patients
- 6 Graft loss/failure in 4 patients
- 14 events of renal dysfunction/failure/increased creatinine in 14 patients
- 38 infections events in 27 patients
- 21 events related to the surgical or post-surgical procedure in 18 patients

The DSMB reviewed safety data specifically for cardiovascular, eye, infection and GI events due to an imbalance in the safety reports. They decided the imbalance was due to excess reports of e.g.,"tachycardia", "mild vomiting" and no serious safety signal was found. Overall, the DSMB concluded that the compound was safe to use.

Considering the efficacy data for DGF the DSMB concluded that the best group is 0.5 mg/kg; this dose showed an even greater difference from placebo for fDGF. However, a sample size re-estimation for DGF showed an additional >5,500 per group (optimal OPN-305 dose vs. Placebo) would be needed in Part B. Similarly, an extra 100 patients per group would be required if fDGF was to be the primary endpoint. The DSMB, therefore, recommended that the study should stop for futility as significance cannot be achieved with a realistic number of patients.

The DSMB stated that a combined endpoint of DGF + fDGF might be interesting to explore further in ECD Patients. This endpoint showed a 17.6% difference between the 0.5mg/kg dose group and placebo: 64.7% (0.5mg/kg) vs. 82.4% (placebo) in the patients with ECD donors.

All patients EU and USA with ECD Donors (n=68)

	Placebo n=17	**0.5mg/kg n=17**	**1.5mg/kg n=18**	**5.0mg/kg n=16**	**All n=68**
DGF	41.2%	29.4%	33.3%	43.8%	35.3%
fDGF	41.2%	35.3%	44.4%	50.0%	43.1%
EGF (DGF +fDGF)	82.4%	64.7%	77.7%	93.8%	78.4%
Difference from placebo		**17.7%**	4.7%	-11.4%	4.0%

Study Part B: The interim sub-group analysis showed that the most effective dose group was 0.5 mg/kg and therefore this is the dose that will compared to placebo in Part B. The combination of DGF and fDGF provides a more objective endpoint and is a measure of early graft function than DGF alone. The population will be confined to ECD recipients as, particularly in Europe, the DGF rate was as predicted and they appeared to represent a more homogeneous group. An additional secondary endpoint of slow graft function (SGF, defined as a serum creatinine >3 mg/dL on post-operative day 5, but no need for dialysis post-transplant) will also be assessed as a secondary endpoint.

Study Design: This is a three-part, group sequential, adaptive, Phase II study to assess the safety and to evaluate the clinical effect of single intravenous doses of OPN-305 on renal function in patients scheduled to receive a kidney transplantation. Based on the findings from Part A, Part B of the study will compare OPN-305 at a dose of 0.5 mg/kg to placebo given as a single one-hour infusion to patients receiving allografts from ECD donors.

A maximum of 204 patients are expected to be randomised in a double-blind manner 102 to 0.5 mg/kg OPN-305 and 102 to placebo. All patients who are randomised and receive both OPN-305 or placebo and a renal transplant with an ECD kidney will be included in the analysis. Patients who are incorrectly randomised or do not receive an ECD kidney will be replaced. All patients should receive induction therapy for immunosuppression and may or may not be machine perfused.

Randomisation will be 1:1 between 0.5 mg/kg OPN-305 and placebo; patients will be stratified according to whether they are enrolled in the USA or Europe, whether they receive machine perfusion or not and whether they receive basiliximab or ATG as induction.

There will be a review of early graft function by the DSMB after 31 patients have been enrolled in each group who have reached at least 7 days post-transplant; a formal test of futility will be conducted.

An interim analysis will be done after 51 patients have been enrolled in each group who have reached at least 7 days post-transplant; a formal test of futility will be conducted and a decision on continuing the study will be made based on whether a sample size re-estimation will alter the number of patients required to complete the study.

OPN-305-103 study

The goals of the study are:
To assess out to one-year the clinical status of patients who completed the double-blind part A or B of the 6-month study period in the Opsona phase II protocol (OPN305-102) by recording the following:

- Incidence of allograft rejection or loss
- Initiation and frequency of dialysis or other renal replacement therapy (RRT)
- Estimated GFR at the end of the 6-month follow-up period based on a determination of serum creatinine by the local study site
- Incidence and type of serious adverse events (SAEs)
- The occurrence of infections by type and actual organism
- The incidence of hospitalisations

Databaselock for the follow up in OPN305-102 Part A occurred in late May 2015, results for OPN305-103 are also included in this database lock. Interim Clinical study report is pending no data is available for reporting.

OPN-305-104 study

Primary Objective: To assess out to one-year the clinical status of patients who completed the phase 0 part of the Opsona phase II protocol (OPN305-102).

Secondary Objective: None

Study Design

All patients entered in this follow-up study were to attend a 3-month, 6-month 9-month and 12-month post-transplant study visit (the time relating to date of transplant in the phase II trial [OPN305-102]).

A Data Safety Monitoring Board (DSMB) oversaw the study.

Schedule of Assessments and Procedures: Patients were asked to give written informed consent to participate in the follow-up study at the completion visit of Phase 0 in the phase II study (OPN305-102) but a window of 1 week was permitted to allow for any unforeseen circumstance(s).

All follow-up visits: If no routine, or for-cause visit was scheduled within 1 month either side of each 3-monthly visit then a study-specific visit had to be scheduled for the patient to come to the study site. Where routine or for-cause visits occur outside of the time window permitted for the protocol visits then the relevant CRFs were to be completed for each visit.

Withdrawal: If a patient withdrew from the study the Investigator was to try to complete an end-of-study evaluation if the patient agreed.

Safety: Significant safety issues were to be discussed at DSMB meetings or *ad hoc* meetings in the event of treatment-related significant toxicity or serious adverse events (SAEs).

Results

Safety results:

6 of the 8 patients enrolled in OPN305-102 consented to participate in this follow-up study

There were no adverse events (AEs) considered related to OPN-305 in the 6 patients studied. There were 13 AEs types reported on one or more occasions in 5 of the 6 patients; most of the AEs were slight or moderate in intensity. Seven of the AEs were reported as serious adverse events (SAEs) because the patients concerned were hospitalised.

Hospitalisation occurred on one or more occasions for 4 patients.

Pharmacokinetic/ Pharmacodynamic results: Not Applicable (N/A)

Efficacy Results: N/A

In September 2014 the MABSOT consortium submitted a request seeking a further project no cost extension to facilitate the completion of Part B of the OPN305-102 clinical study. Further to an independent review (conducted Feb 25th 2015) of the extension request the Commission

notified the Consortium on April 24th 2015 that the request to modify the grant agreement seeking a further extension of the duration had been rejected.

As previously indicated OPN305-102 is a global clinical study involving multiple clinical centres in Europe and the USA. The EU funding allocated to the MABSOT programme under clinical trial work package 6 covered only part of these costs with the remainder covered by Opsona's venture capital consortium as detailed in section B2.4.1 of Part B Annex One. Further to approval of the redesign of Part B of the OPN305-102 study by the US Food and Drug Administration (FDA) and various competent authorities in Europe (BE, CH, CZ, ESP, DE, NL, PL, UK) Part B of the clinical study will continue such that the all participating clinical centres will be funded directly by Opsona Therapeutics. Part B of the OPN305-102 study commenced in April 2015.

As Part B of the trial has only recently commenced (April 2015) and will not be funded by the EC, no data is reportable for this document.

4. POTENTIAL IMPACTS (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and the exploitation of results

Potential Impacts:

The MABSOT project is designed to progress the development of this Orphan Medicinal product (OMP) through Phase I and II clinical trials. The successful completion of the programme will allow the continued development of OPN-305 as an OMP for the treatment of DGF in a range of solid organ transplant situations. OPN-305 development will have significant benefit to these patients and health care providers:

- Reduced hospitalisation of patients post transplantation due to reduced incidence of DGF
- Enhanced longevity associated with the transplanted organ as a consequence of reduced potential for organ rejection (post 1yr transplantation)
- Reduction in health care costs associated with the management of solid organ transplant patients. In a retrospective study, patients who developed DGF after cadaveric renal allografting, the average hospital stay was 10 days longer than for patients with early graft function. Given the health economic impact of DGF in the renal transplantation setting, interventions that reduce the incidence or prevent the development of DGF should improve the cost-efficacy of the transplantation procedure.
- Enhanced quality of life for solid organ transplant patients

Additional impacts may include:

- The identification of an early biomarker of kidney damage allowing earlier intervention therapies, such as OPN-305 for patients.
- Improvement of graft survival rates and graft function, reducing transplantation waiting times and allowing more marginal donors and grafts from high DGF risk patients to receive transplants.
- OPN-305 will provide the scientific community with a tool for the investigation of TLR2 receptors in DGF and organ rejection.

Further to the overview provide above the following section will examine in further detail the potential benefits of the successful development of OPN-305 as a therapeutic for the prevention of delayed function (DGF) following solid organ transplantation.

Medical Benefit.

To date, DGF preventative measures aim to minimise the number of risk factors identified that predispose to DGF following renal transplantation, in addition to HLA matching to prevent rejection. Risk factors are related both to the donor as well as to the recipient. Nevertheless, DGF occurs in 21-50% of the recipients of a cadaveric renal graft and in 6% of recipients of living donor renal grafts.

To date, no specific drugs exist to prevent DGF. DGF is treated with dialysis until the renal

tubular cells recover from the I/R injury as the renal function improves in terms of urine production and clearance of specific substrates (e.g. minerals, creatinine, urea), as well as its capability to maintain the homeostasis of the recipient.

Given the need for solid donor organs, preservation of organs is necessary to allow sufficient time to match the donor organ to the recipient, to transport and prepare the recipient and the donor organ prior to transplantation. From a pathophysiological point of view, the surgical removal, storage, and transplantation of a solid organ from a donor profoundly changes the homeostasis of the interior environment of the organ. As a consequence, the return of normal organ function is delayed or prevented after transplantation is completed. Donor organ injury is primarily as a result of ischaemia and hypothermia (cold ischaemia time - CIT) and subsequent reperfusion following the transplantation of the organ (I/R injury) in the recipient.

Hence the medicinal treatment strategy to minimise donor organ injury and subsequent risk of delayed graft function (DGF) and its sequelae is two-fold:

1) Non-specific methods using preservation solutions that serves to stabilise the cell membrane and physiological function of the cells during cold storage. These have a significant shortfall in preventing DGF.
2) More specific methods aimed at blocking recognised pathogenic pathways activated by I/R insult reperfusion and which often lead to recruitment of the soluble and cellular components of the inflammatory response, which becomes apparent after transplantation into the recipient, and is aimed to reduce further the incidence of DGF. In this case treatment involves the administration of OPN-305 given systemically by intravenous bolus injection or slow intravenous push just before reperfusing the transplanted ischaemic solid organ.

Hence, OPN-305 will be intended for the prevention of DGF following the transplantation of solid organs that are usually stored/transported in the presence of preservation solutions from harvest to transplantation. OPN-305 is not intended to replace the need for preservation fluids but will be used in conjunction with them. There is as yet no specific method in routine clinical practice used for this purpose. Moreover, OPN-305 may be used in addition to the range of immunosuppressive drugs indicated for the reduction of allograft rejection directly (anti-inflammatory properties) and indirectly (prevention of DGF).

Prevention of DGF

Significant benefit using OPN-305 to prevent I/R injury and DGF in solid organ transplantation is illustrated by the potential benefit in the prevention of DGF in renal transplantation. It should be clear however, that to date no treatment to prevent DGF has been approved in the EU for use in solid transplantation. Hence, the use of OPN-305 and its potential benefit cannot be compared to other medicinal products *per se*. Furthermore, it is not intended to replace the need for preservation solutions but rather to lower further the incidence of DGF and its later consequences.

Recipients of a solid donor organ are at risk of developing DGF though preservation solutions are used as standard procedure, depending on both donor and recipient risk factors. Minimising the number of risk factors for DGF, however, is not satisfactory because not all factors can be

excluded in the selection of the solid donor organ and its recipient, as HLA matching, waiting lists and the antecedent medical condition of the donor and recipient play important roles.

The incidence of DGF following renal transplantation is highly unsatisfactory because DGF, caused in large part by I/R injury, predisposes to acute rejection of the allograft, haemorrhage and reduction of graft survival. The patient requirement for dialysis and management of DGF prolongs hospitalisation as compared to patients who had an immediate functioning of their renal graft; this increased hospitalisation period impacts on the associated health-economic cost.

OPN-305 may therefore, as highlighted in the setting of renal transplantation, lead to the:

- Reduction in the number of patients receiving medical treatment for graft dysfunction (e.g. requiring dialysis, extra-cardiac mechanical support and/or use of inotropic drugs)
- Reduction of the overall number of recipients with failed grafts
- Reduction of the occurrence of acute and chronic allograft rejection
- Improvement of the longevity of the graft
- Reduction of mortality (in elderly renal graft recipients, in recipients with primary cardiac dysfunction following transplantation
- Reduction of prolonged hospitalisations, including intensive care stay
- Reduction of health economic costs

Quality of Life and health economics in Renal Transplantation

Given the importance to both private and public funding bodies in evaluating health benefits of new drugs or treatment regimes in kidney transplantation it is not surprising that a vast number of studies in this area have been performed. This section will briefly examine costs associated with transplantation verses dialysis, the economic impact of delayed graft function (DGF) and types of donor kidney in order to illustrate the significant impact the successful development of OPN-305 as a treatment for DGF in kidney transplantation is likely to have.

i. <u>Transplantation v Dialysis</u>
   - Based on quality of life (QoL) measurement and cost benefit analysis it is clear that transplantation significantly improves patient QoL and costs significantly less than patients that remain on dialysis. For example figures for the UK in 2009 demonstrate that the cost benefit of kidney transplantation compared to dialysis is £24,100 per year for each year that the patient has a functioning transplanted kidney; similarly cost savings of $27,000 per year for each patient who has a transplant instead of remaining on kidney dialysis have been shown in the USA (Uni. of Maryland).

ii. <u>The Economic impact of DGF</u>
   - Studies in the USA have shown that DGF is associated with up to $25,000 higher cost per patient than when there is no DGF.

   - In addition, patients who experienced DGF and received dialysis in >2 early periods were more than twice as likely to lose their grafts within 3 years as those without early dialysis requirements.

iii. <u>Donor type</u>

Saidi et al 2007 retrospectively examined 271 deceased donor kidney transplants performed at Massachusetts General Hospital between Jan 01 1998-Dec 31 2005. Of the 271 kidneys examined 163 were SCD, 44 ECD, 53 DCD and 11 ECD/DCD. The study found that DGF rates were significantly higher in ECD and DCD kidneys compared to SCD. Early (12 and 24 month) graft survival rates were comparable between groups, however after a mean follow up of 50 months graft survival was significantly less in the ECD groups compared to SCD and DCD, 65%, 79% and 80% respectively (p=0.0116), this may be related to the finding that in this study the DGF rates were highest in the ECD and ECD/DCD patients than SCD and DCD although the study failed to show a positive correlate (p=0.44).
The data also showed that the utilization of ECD, ECD/DCD and DCD kidneys was associated with higher initial hospitalization charges. These kidneys had a higher incidence of DGF that required dialysis and also longer length of stay (LOS). This difference in initial hospitalization charges for ECD, ECD/DCD and DCD kidney recipients compared to SCDs, $70,030, $72,438, $72,789 and $47,462, respectively ($p < 0.001$), continued to escalate as more re-admissions were required during the peri-transplant

Another study by Whiting et al 2000 compared the cost of hemodialysis with ECD kidneys from cadaveric donors. The study examined 42,868 cadaveric transplants from the UNOS registry between1991-1996. The authors observed that the breakeven point at which transplantation became more costly than hemodialysis ranged from 4.4 years for SCD to as long as 13 years for ECD kidneys transplanted into high risk patients (high risk classified as those patients >60yrs of age or patients receiving a second transplant)

In another study by Buchanan et al 2008 The United States Renal Data Systems database was analyzed for adult deceased-donor kidney recipients transplanted from 1995 to 2004 who had Medicare as their primary payer. A total of 41,049 transplants were analyzed, including 83.2% from SCDs, 14.2% from ECDs, and 2.6% from DCD donors. The incidences of DGF were 23.6% for SCD, 35.9% for ECD, and 44.2% for DCD donor recipients. The occurrence of DGF was associated with an average $20,000 increase in cost during the first year after transplantation, regardless of deceased-donor category. For patients who did not experience graft failure, DGF was most costly for ECD followed by DCD and then SCD kidney recipients (additional cost of $12,145, $11,692, and $9648, respectively). http://www.medscape.org/viewarticle/578683

The impact of OPN-305 in this particular group of donors is particular relevant. Part A of the OPN-305-102 clinical trial (WP6) suggested that OPN-305 at a dose 0.5mg/kg has potential to improve renal outcomes in ECD kidneys.

Part B of the clinical study which commenced in April 2015 will compare OPN-305 at a dose of 0.5 mg/kg to placebo given as a single one-hour infusion to patients receiving allografts from ECD donors.

Given the high propensity of ECD donors to DGF and that up to 50% of ECD kidneys are discarded the health economics benefits of a successful outcome for OPN-305 in Part B of the trial would be significant

Gender related issues

OPN-305 can be administered to both males and females. OPN-305 is currently dosed to males and females recruited to the OPN305-102 study subject to certain inclusion/exclusion criteria. Nyberg et al 1997 which retrospectively examined 1000 kidney transplants observed that 60% were male and 40% females, recent statistics in both the USA and Europe would indicate that this ratio has remained relatively constant over time.

Nevertheless there is experimental evidence to suggest that male recipients are more susceptible to DGF than females. Levine et al 2015 (Abstract at the American Transplant Congress) noted that in a retrospective analysis of deceased donor renal transplants from 128,493 patients between 1997-2011 male recipients had a DGF rate of 27.1% compared to 21.8% for female recipients. Similar findings have been reported by Chapal 2014, Boom 2009 and others indicating gender is an independent predictive factor for DGF with male recipients more susceptible

As such the use of OPN-305 in the prevention of DGF may be slightly more benefit to male compared to female kidney transplant recipients but this can be looked at as part of a post hoc clinical analysis

Racial Issues

DGF and graft failure rates are known to be higher in blacks than in Caucasians or Asians (Ojo 1995, Feldman 1998), as such the prevention of DGF by OPN-305, while benefiting all donor recipients, would be predicted to have a higher impact on donor recipients of African origin.

Paediatric Transplant Recipients

Paediatric transplant recipients receive 'the best' available kidneys and have low rates of DGF in relation to their adult counterparts which can be attributed to a number of key differences between kidney transplants in children and adults as follows:

i) Children do not receive kidneys from Extended Criteria Donors (ECD)

ii) For deceased donors preference for (deceased brain donor) DBD over deceased circulatory donors (DCD).

iii) Majority of deceased donors for paediatric recipients are <40yrs old

iv) Many countries such as the UK, Austria, Switzerland and the Scandinavian countries have a high proportion of living donors LD.

As such the numbers of paediatric patient receiving kidneys which are at high risk of developing DGF is already very low and with exclusion of ECD and improved access to living donors this rate is likely to become progressively lower over time. As such the impact of treatment with OPN-305 in paediatric recipients is anticipated to be relatively low.

Secondary Impacts

This application of OPN-305 in the prevention of DGF in renal transplants may also translate into positive medical benefits for other solid transplant given all transplant involve an I/R event. TLR2 has also been implicated in lung, hepatic and cardiac I/R injury (Jin et al., 2007, Arslan et al 2010 and 2012). The future development of OPN-305 may therefore entail further clinical studies using OPN-305 in the prevention of I/R injury of solid organs other than the kidney.

Furthermore, as the upregulation of TLR2 post transplantation is associated with organ dysfunction and in many cases graft rejection, the use of OPN-305 may negate or minimise the need for wide-acting immunosuppressants to prevent graft rejection, which are often associated with severe complications, including an increased risk of infections and malignancy (in particular lymphoproliferative disorders) and nephrotoxicity. Therefore, OPN-305 is a novel strategy for preventing DGF and associated allograft rejection in solid organ transplants.

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Dissemination and Exploitation

The following section will describe in brief how the project results have been disseminated hitherto fore and plans for future dissemination activities. This deliverable will also detail the foreground arising from the project and future dissemination plans thereto.

MABSOT Dissemination Plan

On the basis of the expected impact of the MABSOT project, the leading components of our dissemination plans are directed towards different communities:

1. The scientific research community
2. The clinical research community
3. The clinical and health professional community
4. The investor community
5. The Pharma community
6. Patient community

Dissemination Activities

1) The Project has been published nationally (Ireland) & internationally through various forums (press releases, scientific meetings, conferences, investor VC syndicates etc, payer community, pharma community.
2) The project is also publicized via the project website, www.mabsot.eu which also contains a short video produced by the Commission which further details the goals of the project. And is has also been further disseminated using the project twitter account, @FP7MABSOT
3) WP6: Publication of the Phase I data in a high impact open access journal. The manuscript was made 'freely' available (in line with Special clause 39) following payment of a fee to the Journal by Opsona and can be accessed using the following link http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3805945/

a. Further dissemination of the clinical trial will occur via Opsona's web site, international meetings and publication of clinical results, publication of Phase II data is not anticipated until the end of Part B of the Study (study to finish by Q1 2017, publications arising from the trial by Q3/4 2017).

4) Publication plans for the non/pre-clinical elements of the project:

a. There are no plans to publically disclose the results of the non-clinical studies (WP1) or the IMP manufacture (WP2) although in both cases the results from these WPs have been discussed with both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA)
b. WP3: The results arising from the chronic rejection studies may be suitable for publication in a peer reviewed journal. Discussions may be initiated with KCL to explore this possibility further.
c. WP4: In lieu of the finding in both mouse and human clinical samples that SAA does NOT appear to correlate with renal injury there are no plans to publish the results of this WP.
d. WP5: As a correlation between renal function and either SPP-1 or TIMP-1 was not observed in the human clinical samples from patients in Part A of the OPN-305-102 study there are no plans to publish the results from this WP at this time. However this may form part of the final clinical data publication

Exploitation

1) National filing of OPN-305 patent (*Humanised antibodies to Toll-like receptor 2 and uses thereof*), which provides cover for the use of OPN-305 irrespective of the disease application in 14 jurisdictions worldwide. The patent has now been granted in Australia, Europe, Mexico, New Zealand (parent and divisional patents), South Africa and the USA. Granting of the patent in China is expected later in 2015 and in all further pending jurisdictions within the next 1-2 years. The patents can be located using the following URL:
http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=1&ND=3&adjacent=true&locale=en_IE&FT=D&date=20141031&CC=NZ&NR=615441A&KC=A

2) Potential competitor compounds have been identified, the progress of which will be monitored. It is ultimately anticipated that OPN-305 will be exploited by a potential acquirer in order to commercialize the antibody.

5. THE ADDRESS OF THE PROJECT PUBLIC WEBSITE, IF APPLICABLE AS WELL AS RELEVANT CONTACT DETAILS.

Project website: www.mabsot.eu

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