A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (Trial H5: MP0420)

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Appendix H5: MP0420 – version 2.0 (09 April 2021)

The content of this appendix is confidential and should only be viewed by persons covered by the CDA entered between Molecular Partners/ Novartis and NIAID in relation to the TICO / ACTIV-3 study.

This appendix provides detailed information pertaining to the study of this investigational agent. If not stated otherwise, the text in the master protocol gives the approach that will be taken to study this agent.

H.5.1. Introduction and rationale for studying the agent

MP0420 (INN ensovibep) is a multi-valent DARPin® molecule (designed ankyrin repeat protein), consisting of 5 DARPin® domains[1]. MP0420 simultaneously and specifically binds to 3 epitopes in the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein with three different domains and two domains that bind to human serum albumin. This multi-valent binding leads to potent neutralization of SARS-CoV-2 in live virus assays, preventing subsequent viral entry into human cells and viral replication[1]. The multi-valent, cooperative binding leads to extremely high potencies with affinity in the picomolar range and is expected to be effective against mutational escape. The two DARPin® domains which bind to human serum albumin (HSA) increase the half-life to that of a human antibody in the range of two-three weeks[2, 3]with no anticipated change of DARPin® concentration even in case of significant variation of body weight or albumin levels.

MP0420 is produced in *E.coli*-based fermentation, which decreases cost and complexity compared to antibody production. DARPin® molecules, including MP0420, do not require glycosylation or extensive post-translational modification by producer cells, making simple, highly scalable bacterial fermentation feasible[4]. No ingredients of animal origin are used in the fermentation of MP0420. *E.coli*-based fermentation is also used extensively when manufacturing other proteins including Neulasta, Lantus, and Lucentis.

Whereas one antiviral agent (remdesivir), a polymerase inhibitor, has been demonstrated to have clinical benefit in hospitalized patients with mild to moderate disease and is now part of standard-of-care (see Appendix I), treatment options for hospitalized COVID-19 patients are still limited. It is plausible that additional antiviral effects could be produced by the combination of MP0420 with remdesivir and hence, contribute to improvement in time to sustained recovery.

Study MP0420-CP101, a Phase I, randomized, double blind, placebo-controlled, single ascending dose study of MP0420 in 24 (8 per cohort) healthy volunteers is underway. The first two dosing cohorts were completed (3 mg/kg, 9 mg/kg) at the end of 2020 with a third cohort of 20 mg/kg planned to commence in Q1 of 2021. The primary objectives include safety and tolerability and secondary objectives include characterization of pharmacokinetics and the development of anti-drug antibodies. Please refer to the

Investigator Brochure (IB) for preliminary safety and efficacy data from the first two cohorts (3 mg/Kg and 9 mg/Kg).

H5.1.1 *Potential benefits and risks from MP0420*

Potential benefits

The potent antiviral activity of MP0420 has the potential to reduce the viral load of SARS-CoV-2, which could translate into beneficial clinical effects. This statement is supported by preclinical studies summarized below. MP0420 demonstrated high affinity binding to its target, the RBD in the spike protein of SARS-CoV-2, with no observed off-target binding as measured in Retrogenix assay and GLP TCR study [5]. MP0420 has been shown to potently neutralize SARS-CoV-2 in live virus assays. In addition, several known spike mutations did not affect the antiviral activity of MP0420 in neutralization assays using VSVG-pseudotypes [5, 6]. MP0420 was shown to neutralize variants of the UK originated lineage B.1.1.7 (del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H) and the South African originated lineage B.1.351 (D80A, D215G, E484K, N501Y, A701V) as efficiently as the wild-type Wuhan virus with IC50 values in the low single-digit ng/mL range. MP0420 also gave potent protection against individual mutations reported in currently circulating SARS-CoV-2 strains: N501Y, E484K, K417E, Y453F, D614G, S477N, A222V, G446V, G476S, T478I, P479S, V483A, Q493K and F490S.

Significant reduction in viral load and pathogenesis was observed in five studies conducted using two hamster models. MP0420 dose-dependently reduced virus titers in the lung, throat and nasal turbinates. Disease-related body weight loss was reduced and a protective effect on lung tissues was observed. Please refer to the IB for details [5].

Potential risks

Anticipated risks are predicted to be low based on preclinical data, clinical data from four other DARPin® molecules (highlighted below) and initial safety and PK data from a Phase 1 First in Human dose-escalation study support this prediction. The Study Review Committee from the Phase 1 study reported that the overall tolerability was acceptable in both of the first two cohorts with no Serious Adverse Events and permission was granted to enroll the third cohort. The first two cohorts were comprised of 6 “active” plus 2 placebo subjects treated at 3 mg/kg and 9 mg/kg respectively via a single 1-hour i.v. infusion. The study outcomes remain blinded. One participant experienced mild ALT-elevation (less than 2x upper-limit of normal) in conjunction with an episode of likely unrelated diarrhea, a second reported a headache, and a third participant an erythema at the injection site which resolved on same day.

Preliminary PK data from the 3 mg/kg and 9 mg/kg cohorts of MP0420-CP101 indicate a half-life of 2-3 weeks in humans, which is consistent with predictions based on studies in mice, rats, hamsters and cynomolgus monkeys in which the systemic half-lives were close to the species’ serum albumin half-lives, reflecting the intended binding of MP0420 to serum albumin. Please refer to IB for details.

MP0420 is designed not to interact with the human immune system and binds specifically to a foreign viral protein without homology to any human protein. The absence of off-target binding to 5835 human cell surface and secreted proteins has been obtained with

the Retrogenix binding platform. In addition, a Good Laboratory Practice (GLP) study to characterize cross-reactive binding of MP0420 to a panel of FDA- and EMA-recommended normal human tissues found that there was no biologically relevant binding.

GLP toxicology studies have not been performed as there is no relevant species for such studies: sequence homology studies show no homology between the target bound with high specificity by MP0420 on the SARS-CoV-2 virus and any protein of the animal species used for GLP safety studies. Nevertheless, limited safety evaluations have been made in non-GLP studies in mice, rats and cynomolgus monkeys as well as in SARS-CoV-2 infected hamsters and MP0420 was well-tolerated in all cases [5].

Clinical experience is available for four other DARPin® molecules. Abicipar, the first DARPin® used in humans, targets VEGF-A and is in late-stage development as a treatment by intravitreal injection for age-related macular degeneration[7]. No signal for systemic safety concerns was identified in a Phase 3 program where 1258 patients were treated with abicipar over 52 weeks. There was an initial high incidence of local inflammatory reactions, addressed by improving the purification process.

Three other DARPin® molecules are being developed and have been administered intravenously in Phase 1-2 studies to more than 100 cancer patients. Those three molecules are identified as MP0250 (which targets VEGF and HGF), MP0274 (which targets two HER2 domains) and MP0310 (which targets 4-1BB activation with tumor targeting and tumor-localized activation via FAP-binding). For those three molecules, the safety profiles in the individual studies pointed to general side-effects as expected from other biologics or any “foreign protein” medication, i.e. occurrence of infusion related reactions (IRRs). The nature and onset time of IRRs was compound-specific, with frequent IRRs at the first infusion observed with MP0274, IRRs typically starting at the 2nd or 3rd infusion with MP0310 (where occasional IRRs also reported at first infusion), and only very infrequent IRRs with MP0250. All IRR events were manageable with routine intervention, using antihistamines, NSAIDs and occasionally, corticosteroids. Otherwise, the safety profile was driven by the target-related effects rather than the DARPin® nature of the compounds. The anti-VEGF MP0250 was associated with a high incidence of hypertension and proteinuria, while no treatment-emergent hypertension or proteinuria were observed with MP0274 or MP0310, indicating that the events observed with MP0250 could not be attributed to the DARPin® chemical structure per se. Exposure was mostly limited to a few weeks or months as expected for Phase 1 studies in oncology, but no additional safety concerns were identified in individual patients who remained on DARPin® therapy for longer periods (longest duration of 60 weeks and a median duration of 9.7 weeks ref. IB 7.10.2.3) [5].

As with other proteins and as has been seen with the DARPin class, potential risks for infusion of MP0420 are mostly associated with infusion-related reactions. Signs and symptoms of infusion-related immediate hypersensitivity reactions may include, but are not limited to: anaphylaxis, angioedema, bronchospasm, chills, diarrhea, hypotension, itching, skin rash, shortness of breath, urticarial, tachycardia, and throat irritation or chest tightness. Such reactions can be managed through enhanced clinical monitoring and symptomatic treatment using established clinical practices. None of these have been

reported to date from the ongoing Phase 1 study of MP0420. DARPin related IRRs have been managed with the standard interventions including antihistamines, NSAIDs, and occasional corticosteroids. The proposed single dose use of MP0420 will avert potential reactions associated with multiple doses.

In conclusion, the available clinical experience with DARPins® indicates a general safety profile in line with other biologic drugs, and the absence of safety concerns that could be attributed to the DARPin® chemical structure.

A potential risk is the production of anti-drug antibodies (ADA) which might reduce exposure to MP0420 after two to three weeks. Analysis of PK and ADA are included in the Ph1 CP101 study as well as other planned Ph2 CP204 and Ph2-3 CP302 studies as described in the investigational plan described in the IND held by Molecular Partners. However, as MP0420 treatment is expected to achieve its full therapeutic potential when applied as a single administration, this risk is anticipated to be of little or no clinical significance.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of MP0420 may be found in the Investigator's Brochure(s) [5] and Participant Information Leaflet.

Given the data on MP0420 from the ongoing Phase 1 study, the preclinical toxicology profile, non-clinical and clinical data from 3 other DARPin® molecules, and the limited disease directed therapeutic options for patients with COVID-19 illness, the overall benefit-risk assessment of MP0420 in this study is considered favorable.

H5.1.2 *Motivation for agent selection by the ACTIV Trial Oversight Committee (TOC)*
The ACTIV-2/3 Agent Selection Committee (ASC) reviewed the Molecular Partners agent (MP0420), which contains 3 different DARPins blocking the RBD (like a mAb mixture in one) for highest potency & to prevent viral escape against the SARS-CoV-2 virus and voted in favor of the agent proceeding into ACTIV-3, and the TOC endorsed that recommendation. MP0420 was supported because Molecular Partners presented strong preclinical data for viral neutralization, including the intention to conduct studies on the emerging viral variants of concern with the USG Therapeutics Research labs. Given where the current mutations are, they should not affect the potency of MP0420. Live virus neutralization using MP0420 exceeded the minimum criteria for trial entry, which are IC_{50} <100 ng/ml and IC_{90} <1000 ng/ml. While there was some concern about safety and toxicity with this being a new class of agents, Molecular Partners' early safety and toxicity showed no issues and they plan to complete full FDA-compliant GLP TCR study by early January 2021 [5]. In addition, single dose PK studies in mouse (50 mg/kg), hamster (10 mg/kg) and cynomolgus monkey (10 mg/kg) showed MP0420 to be well tolerated with no clinical signs of adverse effects.

Molecular Partners also provided a strong rationale for their choice of dosing for their agent which was strongly supported by their preclinical dose finding studies in hamsters. MP0420 at 20 mg/kg i.p. at same time as infection resulted in no weight loss and no

deaths (5/6 placebo animals died on Days 2/3). In addition, MP0420 showed a 7-log reduction of lung virus load at Day 3 and an 8-log reduction at Day 5. Molecular Partners showed a solid plan for Phase 1 development of their agent and strong FDA support based on their pre-IND meeting. Finally, the ASC found the manufacturing and scalability strategy for Molecular Partners sufficient for the full trial and beyond now that they have partnered with Novartis to scale up the manufacturing. The agent can be rapidly manufactured in bacteria with high yield production.

Molecular Partners/Novartis' statement regarding plans for licensure: *Molecular Partners and Novartis are* biopharmaceutical companies whose goal is to bring important medical breakthroughs to as many patients in as many countries as possible. It would therefore be *Molecular Partners/Novartis'* general intent to pursue licensure in countries where the trial occurs. In the case of the COVID-19 pandemic, the actual decision to pursue licensure will be impacted by other factors which may include: status of the COVID-19 pandemic in the country and unmet medical need, availability of other therapies including vaccines, available drug supply and other supply feasibility issues, and regulatory considerations.

H5.1.3 Justification for dose chosen for MP0420

The dosing regimen of MP0420 for the ACTIV-3 study was selected by considering a range of data that together predict a single intravenous dose of 600 mg will be safe and efficacious in COVID-19 patients. Factors considered for dose selection included: preclinical safety data, available clinical safety and tolerability results from the ongoing Phase 1 dose escalation FIH study (MP0420-CP101), in vitro and in vivo pharmacology results, observed clinical PK for MP0420 in the FIH study, clinical PK for a structurally similar DARPin (MP0250) and PK/PD modeling. Each of the considered elements is briefly summarized below.

<u>Preclinical and clinical safety for MP0420</u>
The safety-focused NOAEL approach was used to determine first-in-human doses of 3, 9 and 20 mg/kg and a summary of the relevant preclinical safety data can be found in the IB. Dosing of healthy volunteers with single i.v. infusions of 3 and 9 mg/kg (9 mg/kg would equate to a flat dose of 720 mg in an 80 kg person) has been completed and these doses were assessed as safe and well tolerated with no serious adverse effects reported. The 20 mg/kg cohort will be enrolled in Q1 2021. Based on this, the proposed dose of 600 mg (7.5 mg/kg in an 80 kg person) is expected to be safe in ACTIV-3 patients.

<u>Preclinical pharmacology for MP0420</u>
In vitro pharmacology studies demonstrated that MP0420 displays sub-pM binding affinities to the SARS-CoV-2 RBD (SPR assessment) and has IC_{50} values in the range of 10-50 pM (1–5 ng/ml) in SARS-CoV-2 neutralizing assays against wild-type, pathogenic, and pseudo-type viruses. Furthermore, IC_{50} values in the same range for the neutralization of pseudo-type viruses with different spike serotypes suggest MP0420 could be effective against mutational escape. Based on non-clinical pharmacology assessment in SARS-CoV-2 infected hamsters, therapeutic dosing regimen for MP0420 have been identified between 3 and 20 mg/kg. When dosed

during infection (acute) rather than prior to infection (prophylactic) efficacious doses are observed at 9 mg/kg and higher with significant improvement in mortality that was generally associated with a reduction in SARS-CoV-2 viral load

Dose-related lung distribution of MP0420 was demonstrated in healthy mice following single i.v. doses of 1, 10 and 50 mg/kg. Analysis of BAL harvested at 72 h post dose provided evidence for distribution of MP0420 into the epithelial lining fluid (ELF) of the lung. MP0420 concentrations in ELF of 1.8, 6.1 and 44 nM for the dose levels 1, 10 and 50 mg/kg were measured, which is respectively 21, 90, and 80 times lower than measured in serum samples taken at the same time. However, the estimated ELF concentrations are in the range of, or above, the potency of MP0420 against wild-type virus in in vitro assays where IC_{50}s of 0.05, 5 and 5 nM were measured against viral challenge levels of 10^4, 10^5 and 10^6 TCID respectively. In addition, literature data suggests that the vasculature of inflamed respiratory tract epithelium is more permeable to plasma proteins, and thus it is conceivable that MP0420 concentrations in the ELF of COVID-19 patients could be higher than those determined in healthy mice.

Initial human PK results from MP0420-CP101

Ph1 investigation of the safety, tolerability and PK of MP0420 in healthy participants is ongoing. Initial assessments of cohort 1 (i.v., 3 mg/kg) and cohort 2 (i.v., 9 mg/kg) are available. Cohort 3 will be enrolled in March 2021. Based on initial data analysis, the estimated half-life for MP0420 across cohorts is approximately 14.4 days (mean, range: 11.4-24.0 days). Slightly greater than dose-proportional increases in exposure were observed from cohort 1 to cohort 2 (3.8-fold increase in AUC with a 3-fold increase in dose). Cohort 2 exhibited day 14 serum concentrations of 143 ±20.4 ug/mL (mean ±SD), which corresponds to 1690 ±241 nM (mean ±SD), and is >1000-fold above the IC_{50} determined for MP0420 in infected Vero E6 cells.

Human dose projection by PK/PD modelling

The PK/PD model was constructed from publicly available data describing viral kinetics from SARS-CoV-2 patient throat swabs from untreated COVID19 patients and calibrated to describe reported viral load data from patients treated with a neutralizing antibody therapeutic (LY-CoV555). The PK/PD model predicts effects in the lung and makes the following assumptions: 10% of systemic MP0420 rapidly distributes from blood to lung; lung viral kinetics are approximated by throat swab viral kinetics; 60 spike trimers (RBDs) are present on the virus' surface; binding RBD neutralizes interaction with the ACE-2 receptor, which blocks infection; MP0420 has a Kd = 1 pM (based on SPR binding data); clearance of DARPin-bound virus is equal to non-DARPin-bound viral clearance; sustained immune response over the duration of viral infection. The model predicts a near-maximal effect on reduction of free spike protein with an MP0420 dose of 75 mg (>95% reduction in free viral spike protein AUC), which is expected to correlate with clinical efficacy. Due to uncertainties in both the modeling predictions and the severity of disease at onset of therapy, an 8-fold margin was applied and a dose of 600 mg was selected.

Thus, the composite of PK/PD modelling, preclinical pharmacology, and clinical safety, tolerability and PK data support the use of 600 mg MP0420 for treatment of COVID-19 patients.

H5.2. Agent specific eligibility criteria

In addition to the inclusion and exclusion criteria outlined in the master protocol, the following patients will be **excluded**:

1. pregnant women
2. nursing mothers
3. women of child-bearing potential who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with men or practice appropriate contraception through 11 weeks after receiving MP0420/placebo
4. men who are unwilling to acknowledge the strong advice to abstain from sexual intercourse with women of child-bearing potential or to use barrier contraception through 11 weeks after receiving MP0420/placebo.

H5.3. Description of investigational agent

H5.3.1. Administration and duration

See the PIM and Pharmacy Procedures for details. See also section H5.5 below for guidance on the clinical management of the infusion, including infusion-related reactions.

MP0420 will be administered intravenously within one hour in a one-time infusion. Specific instructions can be found in the pharmacy procedures.

The recommended infusion rate is ≤5 mL/min to administer the entire content of the infusion bag. The infusion rate may be reduced as deemed necessary if an infusion reaction is observed.

Participants will be closely monitored during the infusion and for at least 2 hours after completion of the infusion. Additional monitoring may be necessary based on clinical judgement of the study investigator(s) and/or site staff, and in accordance with the master protocol. The site must have resuscitation equipment, emergency drugs and appropriately trained staff available during the infusion and for at least 2 hours after the completion of the infusion.

If a participant has not already received the relevant dose of remdesivir at the day of enrolment, and has no contraindications to start remdesivir, it is recommended (but not required) that the relevant dose of remdesivir is infused after the infusion of MP0420/placebo is completed.

H5.3.2. Formulation and preparation

MP0420 is a sterile drug product and is packaged in 20R glass vials.

A total of 4 vials (concentration: 15 mg/mL, extractable volume: 10.0 mL) provides the 600 mg dosing of the agent; the (see Table H5.1). Placebo is normal saline. The study medication is prepared by an unblinded pharmacist at the local pharmacy. To ensure

blinding of the participant and clinical staff a colored sleeve will be placed over the infusion bags used (see PIM and Pharmacy Procedures).

MP0420 should be prepared and dispensed as soon as possible after randomization. Infusions should be completed within 24 hours after the infusion has been prepared by the pharmacist.

Table H5.1. Study medication overview.

Intervention Name	**Placebo**	MP0420
Dose Formulation	0.9% sodium chloride solution	Biologic – DARPin® molecule (10.0 mL extractable volume per vial, 15 mg/ml per vial)
Dosage Level(s) (mg)	Not applicable	600 mg
Route of administration	IV infusion	IV infusion
Use	Placebo	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Commercially available 0.9% sodium chloride solution	Molecular Partners AG, Zurich-Schlieren. Switzerland
Packaging and Labeling	Commercially available 0.9% sodium chloride solution	Study intervention will be provided in 20R single-use glass vials individually packaged in a carton, and labeled appropriately.

H5.3.3 Supply, distribution, and accountability
Procedures for ordering and accepting drug, for maintaining inventory of MP0420, and for breaking the blind in the event of a medical emergency will be described in the Pharmacy Procedures.

H5.3.4. Contraindicated medications
No medication is known to be contraindicated in patients receiving the investigational agent.

H5.3.5. Precautionary medications
The clinical site should have necessary equipment and medications for the management of any infusion reaction (see section H5.5 below).

Premedication for infusions is not planned.

If an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from premedication, the study investigator(s) should determine the appropriate premedication.

The investigators and sponsor may decide to recommend premedication, if the frequency of infusion reactions among participants warrants it. If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants. The decision to implement premedication for infusions in subsequent participants will be made by the investigator and sponsor and recorded in the study documentation. Any premedication(s) given will be documented as a concomitant therapy.

H5.4. Clinical and laboratory evaluations

H5.4.1 Timing of Assessments

Appendix B outlines the clinical and laboratory monitoring. Assessment and reporting of AEs (section 10.1.1), SAEs (section 10.1.2) and unanticipated problems (section 10.1.3) and their severity, causality (section 10.1.5) and expectedness (section 10.1.6) is performed as outlined in the relevant section of the master protocol.

H5.4.2 Immunogenicity Assessments

At the visits specified in the master protocol (Days 0, 28, and 90) venous blood samples will be collected to determine antibody production against MP0420 – 2 one mL serum aliquots. Immunogenicity may be assessed by a validated assay designed to detect ADAs in the presence of MP0420. Antibodies may be further characterized for their ability to neutralize the activity of MP0420. Remaining volume from the PK sample may also be used for immunogenicity assessments as needed.

H5.4.3. Pharmacokinetic Assessments

At the visits specified in the master protocol (Days 0, 1, 5, 28, and 90) venous blood samples will be collected to determine MP0420 serum concentration for pharmacokinetic assessment. The PK/Immunogenicity assessment will require 2 mL of the serum collected, as described in the Master Protocol Appendix B as “Research Sample Storage”. PK samples may be assessed by a validated assay at a bioanalytical lab. The PK assessment will use the same 2 ml serum specified in the Immunogenicity assessment section above (H5.4.2). Analysis of samples from placebo-treated subjects is not planned for PK analysis as placebo is shared across arms. Using a limited amount of placebo samples as negative controls will be possible. Remaining sample used for PK may be pooled and used for exploratory metabolism or bioanalytical method experiments as deemed appropriate. Samples maybe shipped to the lab for analyses in batches as the substudy is unfolding. Results from such analyses will be returned to the trial central database. This data and all other data on the participants will remain in the trial central database until the trial is unblinded.

H5.5. Clinical management issues

All participants should be monitored closely for 2 hours after the infusion, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

H5.5.1. Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction, include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

Infusion-related reactions' severity will be assessed and reported using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected version 2.1 [8].

H5.5.2. Site Needs

The clinical site should have necessary equipment, medications, adequately qualified and experienced staff with appropriate medical cover for the management of any infusion reaction, which may include, but is not limited to, oxygen, IV fluid, epinephrine (adrenaline), acetaminophen (paracetamol) and antihistamine.

The pharmacy procedures and the PIM outline needs of the study site pharmacy and/or local site pharmacy.

H5.5.3. Management of Infusion Reactions including Discontinuation

Investigators will use their clinical judgement and standard of care to evaluate and manage all infusion reactions. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms. If a severe and potentially life-threatening infusion reaction occurs with MP0420/placebo, its use should be permanently discontinued.

If a participant is not infused with MP0420/placebo or the complete infusion is not given, all follow-up procedures and reporting's outlined in the master protocol (Appendix B for overview), should be adhered to as indicated.

H5.5.4. Adverse Events of Special Interest (AESI)

The following are AESIs for the agent MP0420 or placebo:

- Infusion-related reactions
- Allergic/hypersensitivity reactions

H5.5.5. Incident Pregnancy in Participants or Their Partners

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

The participant will continue follow-up in the protocol. The outcome of the pregnancy and reported on the Pregnancy Outcome eCRF.

If an investigator learns that a male participant's partner has become pregnant while the male participant is in this study, the investigator is asked to attempt to obtain information on the pregnancy, including its outcome, after obtaining consent from the pregnant partner. The outcome of the pregnancy will be reported on the Pregnancy Outcome eCRF.

H5.6. References

1. Walser, M., et al., *Highly potent anti-SARS-CoV-2 multivalent DARPin therapeutic candidates.* bioRxiv, 2020.
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4. Stumpp, M.T., K.M. Dawson, and H.K. Binz, *Beyond Antibodies: The DARPin((R)) Drug Platform.* BioDrugs, 2020. **34**(4): p. 423-433.
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