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FINAL RESEARCH REPORT

Comparing Treatments for Resistant Kawasaki Disease – The KIDCARE Study

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ABSTRACT

Background: Kawasaki disease (KD) is a systemic vasculitis that affects infants and children and manifests as an acute illness with fever and mucocutaneous features including rash; injected conjunctivae; cervical lymphadenopathy; oral mucosal changes; and swollen, erythematous hands and feet. Although the fever and acute clinical signs are self-limited, damage to the coronary arteries is a potential lifelong complication. Randomized clinical trials in the 1980s established intravenous immunoglobulin (IVIG) as an effective therapy to reduce systemic and tissue inflammation and prevent coronary artery damage. Among various ethnic and racial groups, 10% to 20% of children have a recurrence of fever after initial therapy with IVIG, are at increased risk of coronary artery aneurysms and need additional anti-inflammatory therapy. A second infusion of IVIG, infliximab, and corticosteroids have all been advocated for treatment of IVIG-resistant KD, which is defined as persistence of fever rather than laboratory markers of inflammation.

Objectives: The primary objective was to test the hypothesis that infliximab would be superior to a second IVIG infusion for treatment of persistent or recrudescent fever for children with KD who did not become afebrile after the first IVIG infusion (resistant KD). Cessation of fever (<38 °C rectally or orally) 24 hours after initiation of study treatment was the primary outcome measure. We also sought to determine whether infliximab treatment would result in more rapid resolution of inflammation, fewer adverse events, improved coronary artery measurements, and shorter hospitalization compared with a second IVIG infusion.

Methods: The Kawasaki Disease Comparative Effectiveness study, a 30-site, randomized, comparative effectiveness crossover trial among infants, children, and adolescents with KD with fever 36 hours or more after completion of their first IVIG infusion, randomly assigned participants to a second IVIG infusion (2 g/kg) or infliximab (10 mg/kg). Participants with fever 24 hours to 7 days after completion of their assigned treatment crossed over to the other treatment group. The primary outcome measure was resolution of fever 24 hours after initiation of study treatment with no recurrence attributable to KD within 7 days after discharge.

Results: Overall, 103 participants were randomly assigned—54 to infliximab, 49 to second IVIG—and included in the intention-to-treat analysis. Two patients randomly assigned to infliximab did not receive the allocated treatment. The primary outcome measure was met by 40 of 52 (77%) and 25 of 49 (51%) participants treated with infliximab vs second IVIG infusion, respectively (P = .0076; odds ratio, 3.2 [95% CI, 1.36-7.52]). Thirty-one participants with fever more than 24 hours after completion of their first study treatment crossed over: 9 (17%) in the infliximab group and 22 (45%) in the second IVIG group. Three participants randomly assigned to infliximab and 2 participants randomly assigned to second IVIG with fever beyond 24 hours did not cross over. Mean (SD) hospital stay was 4.5 (2.5) days for participants in the second IVIG group and 3.2 (2.1) days for those in the infliximab group (P < .001). There was no difference between treatment groups for markers of inflammation or coronary artery aneurysm formation. Of the 58 participants who received IVIG as either their first or second treatment,

19 (33%) had a 2 g/dL or greater drop in hemoglobin concentration (3 needed transfusion) vs 3 of 43 (7%) participants who received only infliximab without crossover (*P* = .003).

Conclusions: When patients with IVIG-resistant KD were treated with infliximab, fever duration and need for additional therapy were reduced, anemia was less severe, and hospitalization was shorter.

Limitations: There was no centralized interpretation of echocardiograms by a core laboratory, and thus the assessment of coronary artery changes stratified by treatment must be viewed with that limitation in mind. Some sites chose to intensify therapy immediately for patients with an abnormal initial echocardiogram (*z* score ≥2.5) or other high-risk features, and therefore such patients were not enrolled in this study.

BACKGROUND

Kawasaki disease (KD) is a vasculitis of unknown etiology that is the most common cause of acquired heart disease in infants and children in developed countries.[1] KD meets the NIH definition of a rare disease and is estimated to affect approximately 6000 children in the United States each year.[2] Treatment with intravenous immunoglobulin (IVIG) reduces the incidence of coronary artery aneurysms (CAAs) from 25% to approximately 5%.[3] However, for 10% to 20% of patients with IVIG-resistant KD (defined as having an oral or rectal temperature ≥38.0 °C ≥36 hours after the end of the initial IVIG infusion), there is no robust evidence base to guide treatment. Perhaps because of the persistence of inflammation, the incidence of CAA is higher in this treatment-resistant group. In a study of 362 patients with KD, 9 of 60 (15%) IVIG-resistant patients developed CAA.[4] Of concern, recent data from Japan suggest that the rates of IVIG resistance rose from 7% in 2003 to 23% in 2014, with a concomitant increase in CAA.[5]

There has been much speculation, but few data, on the mechanism of action of IVIG in acute KD. It is certainly plausible that IVIG interacts with many different parts of the immune and vascular systems downregulate inflammation. The major goal of IVIG treatment of KD is to prevent coronary artery damage and to reduce tissue inflammation. However, IVIG also mediates the rapid disappearance of fever, rash, conjunctival injection, and systemic malaise. Thus, the majority of patients with KD, even those who go on to become IVIG resistant or develop aneurysms, experience a dramatic clinical improvement within hours of receiving the IVIG infusion. Although these rapid anti-inflammatory results certainly benefit patients, it is important to remember that the goal of therapy is to protect the vascular system and myocardium from immune-mediated damage.

Studies of IVIG action, largely from animal models, have demonstrated effects on pathways involving Fc receptors, complement, cytokines, and autoantibodies. Cellular targets include endothelial cells and cells participating in both innate and adaptive immunity.[6,7] Research on the actions of IVIG in KD has been done in children and in animal models, but much of it delineates the phenomenology of IVIG treatment and does not provide a mechanism. Our group has collaborated with immunology colleagues to address this knowledge gap. Work by

Franco et al in collaboration with our group has delineated a role for a population of Fc-specific natural T regulatory cells that expands after IVIG administration and produces interleukin 10 (IL-10) as an anti-inflammatory cytokine.[8,9] A more recent collaboration with the Croker Lab at the University of California, San Diego (UCSD), established that IVIG, through an Fab_2-mediated effect, rapidly kills mature neutrophils that are the major cellular source of IL-1b in the circulation.[10] In the future, it may be possible to make designer peptides based on regions of the Fc portion of the immunoglobulin G molecule that mediate downregulation of inflammation. These could be combined with a monoclonal antibody that targets the neutrophils to achieve global downregulation of inflammation. However, that is many years away; in the meantime, we are faced with practical questions about how to treat patients whose disease is resistant to their first infusion of IVIG.

Resistance to IVIG among some patients with KD was first noted in the initial IVIG trials, which were conducted in the 1980s, and the appropriate therapy for such patients has remained unresolved to the present day. Based on the apparent dose response to IVIG, administration of a second dose of IVIG became first-line therapy for resistant patients, and this treatment is still widely used today.[11] Alternative treatments include infliximab (5 mg/kg), steroids (prednisone 2 mg/kg/day for an extended period), cyclosporine, anakinra, and plasmapheresis.[12-20] The RAISE study in Japan studied IVIG plus IV and oral steroids for high-risk patients with KD, using a scoring system to predict IVIG resistance.[21] The study showed a benefit in favor of steroids for a reduction in aneurysms as defined by the Japanese Ministry of Health criteria. However, the Japanese scoring system did not determine which Western patients were at risk for IVIG resistance.[22] Despite this limitation, steroids gained widespread traction as a treatment for patients with IVIG-resistant KD, but a similar randomized trial of the RAISE steroid regimen has not been performed in the United States. In a 2-center retrospective study of the administration of a second IVIG infusion or infliximab as the first re-treatment, patients with IVIG-resistant KD who were treated with infliximab had more rapid resolution of fever and inflammatory markers, fewer days in hospital, and lower costs of care.[14] There was no difference in coronary artery outcomes between groups, although the study lacked sufficient power to see an effect.

Three published randomized clinical trials compared a second infusion of IVIG with infliximab for patients with IVIG-resistant KD.[13,23,24] All 3 studies (1 in the United States [24 patients], 1 in Japan [31 patients], and 1 in Korea [43 patients]) found a higher rate of fever resolution and shorter duration of hospitalization in patients who received infliximab. A Cochrane review of these studies in 2018 concluded that there was "low certainty evidence that [tumor necrosis factor] α blockade had a beneficial effect on IVIG treatment resistance" because of the small number of underpowered randomized clinical trials.[25] In Japan, a multicenter, prospective, open-label, single-cohort observational study of 291 patients with acute KD refractory to conventional therapy who were treated with a single 5-mg/kg dose of infliximab concluded that infliximab was safe and effective.[26]

There is currently clinical equipoise regarding the best treatment for patients with IVIG-resistant KD who may receive either a second infusion of IVIG with or without corticosteroids, pulse or longer-course corticosteroids alone, or infliximab. Persistent or recrudescent fever after the first IVIG infusion rather than any laboratory measure of inflammation is considered a sign of continuing inflammation, and there is consensus that all such patients should receive additional therapy. Guidelines on KD from the American Heart Association (AHA) assign an evidence level of B (nonrandomized studies) to re-treatment with second IVIG or steroids and an evidence level of C (consensus of experts) to infliximab.[1] Thus, robust randomized clinical trial data to guide treatment are needed. The stakes are high for this subgroup of patients with CAA resulting from persistent inflammation, which may lead to permanent damage to the arterial wall, with an associated risk of myocardial infarction, arrhythmias, or sudden cardiac death.[27]

The Kawasaki Disease Comparative Effectiveness (KIDCARE) trial was designed to determine best practice for a multiethnic, geographically diverse population of patients with IVIG-resistant KD across the United States. The primary outcome measure was the resolution of fever 24 hours after initiation of study treatment with no recurrence of fever attributed to KD in the first 7 days after discharge. Secondary outcome measures included:

- Duration of fever after study treatment;

- Duration of hospitalization after randomization;
- Decreased inflammation, as measured by changes in white blood cell (WBC) count, absolute neutrophil count (ANC), and C-reactive protein (CRP) concentration from baseline, at 24 hours (±2 hours) after completion of the first study treatment, and at study completion (5-18 days after study treatment);
- Change of 0.5 or more SDs between baseline and study completion for the right coronary artery (RCA) or left anterior descending coronary artery (LAD) *z* score, as measured by echocardiography; and
- Comparison of therapy-related adverse events (AEs), as adjudicated by an AE committee.

Specific aim 1 tested the hypothesis that infliximab would be superior to a second IVIG infusion for treatment of persistent or recrudescent fever in children with KD who did not become afebrile after the first IVIG infusion (resistant KD). Cessation of fever (<38 °C rectally or orally) 24 hours after initiation of infusion with no recurrence in the next 7 days was the primary outcome measure.

Specific aim 2 tested the hypothesis that infliximab treatment would result in more rapid resolution of inflammation, fewer AEs, and shorter hospitalization compared with second IVIG. Inflammation was evaluated by the change in WBC count, ANC, and CRP concentration between baseline and 24 hours after treatment and between baseline and 2 weeks after treatment.

Specific aim 3 tested the hypothesis that infliximab treatment would result in a change from baseline in coronary artery *z* worst score of 0.5 or more SDs than second IVIG 2 weeks after treatment, as measured by echocardiography. The *z* scores (internal diameter of the RCA and LAD normalized for body surface area and expressed as SDs from the mean) were calculated from patient height, weight, and internal artery dimensions provided by the sites. *z* Worst was defined as the highest *z* score for the RCA and LAD from the echocardiograms at baseline and at study completion.

Specific aim 4 was an exploratory aim to evaluate patient-reported outcomes (PROs) and use of a parent observation tool to record discomfort, psychosocial concerns, and other experiences of treatment during their children's hospital stay and outpatient evaluation. Patient-reported outcomes were evaluated as a function of treatment group.

PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS

This study reflects direction given by the KD Stakeholder Advisory Board of the patient-centered SCAlable National Network for Effectiveness Research, a clinical data research network funded by PCORI. In 2015, the board set as an aspirational goal a reduction in the percentage of new patients with KD with permanent disability by one-quarter (from an estimated 7% to 5.25%) by 2020. In summer 2015, 116 stakeholders—72 adults who had had KD as children or whose children had KD and 44 clinicians/researchers—participated in an online Delphi consensus panel, a deliberative method for rigorously and statistically determining consensus, to set priorities for research in KD. They determined that the top research priority (of 7 nominated topics) was to "compare medications for infants and children with specific characteristics to determine which ones have the best long-term outcomes with the least risk."

Six members of the previous Stakeholder Advisory Board collaborated with the research team to plan the study and continued as the Study Advisory Board (SAB). The board consisted of 2 co-investigators, an adult who had had KD as a child (Ms Katie Rauschl) and the parent of a child with KD (Ms Anna Lillian), along with 4 others who had had KD or were parents of children with KD (Table 1). The SAB members participated in yearly oversight meetings. In addition, they reviewed the study design, with particular emphasis on specific aim 4. All members of the advisory board reviewed the proposal. They provided detailed input on the domains to be covered in the parent observation tool and how it should be implemented, and they considered options for offering compensation to participants. The SAB helped create and test the questions used in the parent observation tool.

Table 1. SAB[a] Members

Anna Lillian	Parent of child with KD
Cara Rauschl	Parent of child with KD
Catherine Frank	Parent of child with KD, KD Foundation Board member
Kate Davila	Former patient with KD, KD Foundation Board member
Katie Rauschl	Former patient with KD
Vanessa Gutierrez	Parent of child with KD, president of KD Foundation

Abbreviations: KD, Kawasaki disease; SAB, Study Advisory Board.

[a]The SAB provided important input on revision of the parent observation tool (Appendix B), including refinement of their child's signs and symptoms of KD measured in the tool. They reviewed plans for implementing the tool and recommended changes to procedures to streamline data collection and reduce burden for parents. In addition, the SAB contributed to participant recruitment efforts by creating study information published on the Kawasaki Disease Foundation website, writing a letter to include with the study flyer to parents considering participation in the study, and being on call to talk with potential participants. The SAB provided feedback on the analysis plan and endorsed the approach taken for the analysis.

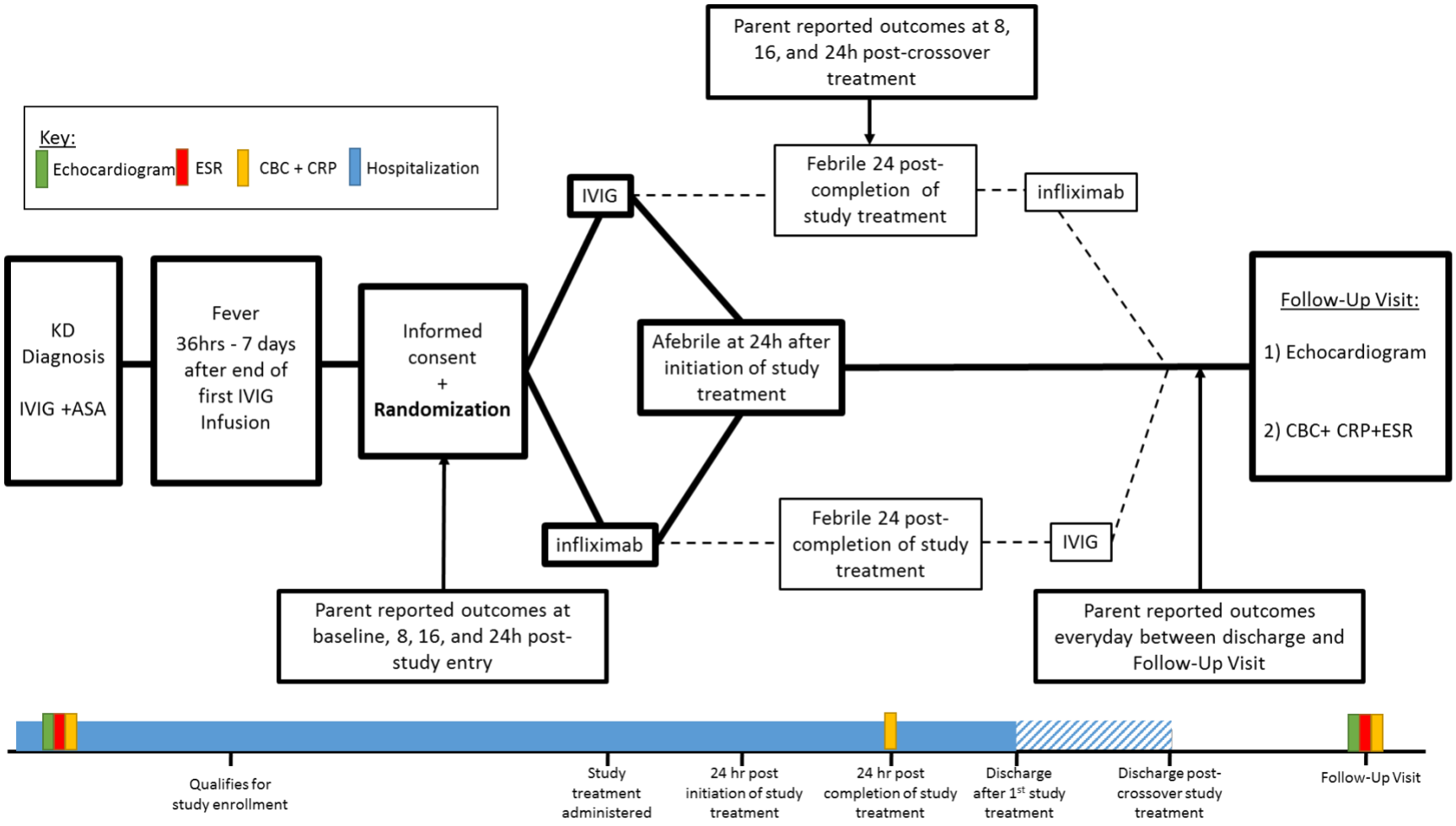
METHODS

Study Overview

This was a 4-year (3.75 years of enrollment), 2-group, randomized, open-label, multicenter superiority treatment study to compare infliximab with a second IVIG infusion for treatment of persistent or recrudescent fever in children with KD who did not become afebrile after the first IVIG infusion. Patients were randomly assigned to receive either infliximab (10 mg/kg) or a second IVIG infusion (2 g/kg).

Study participants who did not become afebrile within 24 hours to 7 days after the beginning of their study-assigned treatment crossed over to treatment with the other study medication. Thus, a participant randomly assigned to receive a second IVIG infusion crossed over to receive infliximab if fever continued or recrudesced at 24 hours to 7 days after the start of the second IVIG infusion and vice versa (Figure 1).

Figure 1. Kawasaki Disease Comparative Effectiveness Study Overview



Abbreviations: ASA, aspirin; CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Thirty sites across the United States participated in the trial. Participants' temperatures were measured by the oral, rectal, or axillary route to accommodate variations in the various sites' hospital and nursing practices. Fever was defined as a temperature of 38.0 °C (measured by oral or rectal route) or 37.5 °C (axillary route). During hospitalization, parents recorded symptoms and other observations of their children at baseline and at 8, 16, and 24 hours after treatment. After hospitalization, parents recorded daily symptoms and daily temperatures at home with thermometers provided at the time of discharge. Symptoms and temperatures were recorded until they returned for their first clinic visit. A broad window of time after discharge was allowed for the first clinic visit (study completion) to accommodate site variations in their standard practice.

Study Setting

We chose 30 pediatric centers across the United States to provide geographic and ethnic diversity in our study population. In this pragmatic trial, our goal was to create generalizable information that would be relevant for all pediatric populations nationwide.

Participants

Patients aged 4 weeks to 17 years who met AHA criteria for complete or incomplete KD and were initially treated for KD with IVIG (2 g/kg) within the first 10 days after fever onset were eligible for enrollment. Incomplete KD was defined according to the AHA 2017 guidelines as fever (temperature ≥38 °C or 100.4 °F) for 3 or more days and 4 or more clinical criteria (conjunctival injection, rash, oropharyngeal changes, extremity changes, cervical lymphadenopathy) or 2 or more clinical criteria with abnormal echocardiogram (*z* score for the diameter of the LAD or RCA ≥2.5) or 2 or more clinical criteria with 3 of 5 laboratory criteria (WBC count ≥15 000, anemia for age, platelet count ≥450 000, albumin ≤3.0 g/dL, elevated alanine aminotransferase, and sterile pyuria). Exclusion criteria included initial treatment with IVIG after the 10th day of fever and treatment with steroids or other medication for intensification of initial therapy. Also excluded were patients with chronic disease (except asthma), atopic dermatitis, autism spectrum disorder, or controlled seizure disorder; patients with known prior infection with tuberculosis, coccidiomycosis, or histoplasmosis or household

contact with active tuberculosis; patients who had used a tumor necrosis factor α blocker within the 3 months before enrollment; and patients with a history of hypersensitivity to infliximab.

All patients who met inclusion criteria were eligible for adjunctive therapy (in addition to IVIG). Therefore, the decision to participate was a question of agreeing to randomization and collection of data. Participants were assigned to a treatment group according to a prespecified randomization scheme stratified by site, sex (male/female), and age (>12 months or ≤12 months) through application of a randomly permuted block randomization design, with a block size of 2 or 4 that was created by the Data Coordinating Center at UCSD, which included principal study statistician Dr Sonia Jain, and her statistical team member, Ms Feng He. The study team created a Research Electronic Data Capture (REDCap) database with restricted access to allow data entry at each participating site. Participant enrollment and randomization through this database were performed by the study site investigators, who could not predict the next treatment assignment.

Patients were recruited by the study principal investigator (PI) at each collaborating site. The site PIs were people who were considered experts in KD care at their respective medical centers. Sites were selected to provide a representative cross-section of the US population with both geographic and ethnic diversity. For parents who declined participation, the PI at each site determined the reason for declining participation.

Interventions and Comparators or Controls

Participants were randomly assigned to either infliximab or second IVIG. In this pragmatic trial, all infliximab or IVIG products were permitted, and the manufacturer's name was recorded. The dosage of infliximab (10 mg/kg) was chosen based on pharmacokinetic modeling that suggested a lower concentration of drug in the tissue compartment when it is administered after IVIG. The infliximab dose was administered intravenously over 2 hours without premedication. The second IVIG infusion was administered according to local practice over 8 to 12 hours. Depending on local standard of care, aspirin dosage was either 30 to 50 mg/kg/day or 80 to 100 mg/kg/day until discharge, and then 3 to 5 mg/kg/day until the

participant completed the study at their first outpatient visit. Participants who did not become afebrile 24 hours to 7 days after the end of their study-assigned treatment crossed over to receive the other study medication. Participants who still had persistent fever after receiving their crossover treatment were treated at the discretion of the local team.

Study Outcomes

The primary outcome measure was resolution of fever 24 hours after initiation of study treatment with no recurrence of fever attributed to KD within 7 days after discharge. Secondary outcome measures included:

- Duration of fever after study treatment;
- Duration of hospitalization after randomization;
- Reduction of inflammation, as measured by the change in WBC count, ANC, and CRP concentration from baseline, at 24 hours (±2 hours) after completion of the first study treatment, and at study completion (5-18 days after study treatment);
- Increase or decrease of 0.5 or more SDs between baseline and study completion for the RCA or LAD *z* score, as measured by echocardiography; and
- Comparison of therapy-related AEs, as adjudicated by an AE committee.

Erythrocyte sedimentation rate (ESR) was compared only at baseline and not after treatment because IVIG causes red blood cells to sediment faster.

Sites were provided with a manual of operations from the NIH-sponsored Pediatric Heart Network. In an effort to standardize echocardiographic imaging, each site submitted a single echocardiogram of a nonstudy patient with KD, and the director of noninvasive imaging at Rady Children's Hospital–San Diego assessed the technical quality. A written assessment of the echocardiogram quality with suggestions for improvement as needed was sent to every site. Participant height; weight; and internal dimensions of the RCA, LAD, and circumflex coronary artery (CX) were recorded at baseline and at study completion. *z* Scores (internal diameter of the RCA and LAD normalized for body surface area and expressed as SDs from the

mean) were calculated by the Data Coordinating Center in the REDCap database. *z* Worst was defined as the highest *z* score for the RCA, LAD, or CX from the echocardiograms at baseline and at study completion.

The study Data and Safety Monitoring Board (DSMB) reviewed AEs and serious AEs (SAEs) by treatment group every 6 months in a closed session attended only by DSMB members and the study statistician. Adverse events were defined as unfavorable changes in health, and SAEs were defined as AEs that resulted in prolonged hospitalization, significant disability, incapacity, or death. Attribution of relatedness of SAEs to study treatments was adjudicated by an AE committee composed of 3 experts in pediatric infectious disease or rheumatology.

Sample Size Calculations and Power

The study was sufficiently powered for a superiority clinical trial. For the primary end point, we assumed 53 evaluable participants per group (total N = 106) in this 2-group trial to yield 80% power to detect a difference between the group proportions of 0.22. We assumed that the reference group proportion (ie, second IVIG infusion group response rate would be 67%, or 8 of 12 patients responding) would be similar to that of our published clinical trial.[13] The infliximab group proportion was assumed to be 92% based on the published clinical trial (ie, 11 of 12 patients responding). The power was computed for the case in which the actual infliximab group proportion of participants responding was lower at 89%. Statistical power was based on a 2-sided, 2-sample binomial test for proportions, and a 2-sided $\alpha = .05$ was used. Study-related observations continued for 2 weeks after administration of the study drug, which introduced the possibility that participants could be lost to follow-up. Assuming 5% attrition, we would have needed to enroll 112 participants to get 106 evaluable patients. The secondary biomarker (aim 2) and *z* worst scores (aim 3) were novel, and there were no similar preliminary data available in the literature to inform sample size.

Time Frame for the Study

Patients were enrolled from March 2017 through August 2020. All study procedures were considered standard of care and were consistent with the usual and customary care of

patients with KD. The 2-week visit (within a window of 5 to 18 days after completion of study treatment) is standard of care in the AHA's 2017 KD guidelines. Thus, compliance with the 2-week visit was high because parents understood that the repeat echocardiogram was important to ensure the safety of their child.

Data Collection and Sources

The project manager, Ms Samantha Roberts, met by Zoom with study coordinators at every site to review data entry procedures. Sites entered participant data into a REDCap database that was specifically created for the trial. Data entry was reviewed every 6 months during the trial, and data queries were returned to the sites.

Parent Observation Tool Development

Our original plan was to use the Face, Legs, Activity, Cry, Consolability scale as a validated outcome measure for the exploratory parent-reported outcomes. It is a measurement used to assess pain for children between the ages of 2 months and 7 years or patients who are unable to communicate their pain. However, in consultation with the SAB, we decided that a more detailed and KD-specific questionnaire would more accurately capture the child's experience in the eyes of the parent. Therefore, we developed a caregiver observation tool to be used both in the hospital and after discharge to capture signs, symptoms, and PROs and the timing for appearance or disappearance of these indicators. These indicators are rarely recorded by clinical personnel but are important in determining the potential burden of the 2 treatment options on patients. The SAB identified domains that were important to capture during hospitalization and during the first few weeks at home, including:

- **Signs.** Presence of rash, bloodshot eyes, general differences in signs between first and second treatments
- **Symptoms.** Sleep, eating and drinking
- **PROs.** Playfulness, smiling, interactivity, responsiveness, disruptions from routine hospital activities

We produced a draft of the tool and conducted cognitive testing of the instrument individually with 6 members of the SAB by phone to ensure relevance of items, clarity, understandability, and length of time estimated to complete the daily observations.[28] When the final tool was completed, we met with the SAB to design a procedure for distributing it on paper or by email (Appendix B).

Analytical and Statistical Approaches

This section briefly describes the planned statistical analysis. Because this was a superiority study design, an intention-to-treat (ITT) analysis was used to analyze the patient outcome data. Results were reported as point estimates (odds ratios [ORs] or mean differences across groups, as appropriate) and interval estimates (95% CIs). All tests of significance were 2 sided. $P \leq .05$ was considered statistically significant. Statistical analysis was performed in R, version 3.6.1 (R Foundation for Statistical Computing). Descriptive analyses were performed to compare baseline characteristics between treatment groups. Laboratory measures were also summarized and compared at each time point. Categorical variables were analyzed via Fisher exact test. Continuous variables were analyzed via Wilcoxon rank-sum test. Safety data, including hemolytic anemia, were summarized overall and by treatment group. Fisher exact test was used to compare the number of participants between treatment groups who experienced any AEs.

Data entry by the sites into the REDCap database was monitored by the project manager at UCSD. In preparation for each DSMB meeting, all sites were audited, and the site coordinator was asked to resolve all missing data queries through the REDCap system. In this way, there were periodic checks to complete data entry and monitor for data entry errors.

Analysis of Primary Outcome (Specific Aim 1)

The study's primary outcome (specific aim 1) was cessation of fever (<38 °C rectally or orally) within 24 hours of initiation of the drug infusion, with no recurrence of fever attributed to KD in the first 7 days after discharge, defined as a dichotomous variable (yes/no). The primary population in the ITT analysis included randomly assigned participants who did not

withdraw consent and had temperature data available. Initially, we had the descriptive Fisher exact test as a primary analysis strategy in the original grant application, but over the years, we modified the primary end point analysis to include univariate logistic regression and multivariable logistic regression to adjust for any potential confounders. This primary end point analysis was described in the approved Statistical Analysis Plan. Logistic regression analysis was conducted with the primary outcome as the dependent variable and treatment group as the main independent variable. Stratification variables and any baseline demographics that were simultaneously unbalanced at baseline and associated with the outcome ($P < .1$) were planned to be included in the logistic regression model as covariates if both criteria were met. However, baseline characteristics were not significantly associated with either study group or outcome ($P < .10$), so they were not included in the multivariable logistic regression model as covariates. A sensitivity analysis was performed with sex (male as the reference group) adjusted in the model as covariate. Crossover summaries describing the outcomes for patients who crossed over to the second study treatment were provided for the randomly assigned participants who did not withdraw consent.

Analysis of Secondary Outcomes (Specific Aim 2)

The first secondary outcome (specific aim 2) tested the hypothesis that infliximab treatment would result in more rapid resolution of inflammation than a second IVIG infusion, as measured by WBC count, ANC, and levels of CRP at 24 hours (±2 hours) after completion of the first treatment and study completion. The Wilcoxon rank-sum test was performed to compare clinical and laboratory variables between groups at the 3 time points: study entry, 24 hours, and study completion. Three separate mixed-model repeated measures (MMRM) models were performed. Participants who were randomly assigned and treated and who had 1 or more corresponding postbaseline inflammation values were included in the analysis. In the MMRM model, the change from baseline inflammation measure was the dependent variable. The independent variables were treatment group, visit (treated as categorical variable), treatment-by-visit interaction, and corresponding baseline inflammation measurement. Stratification variables and any baseline demographics that were simultaneously unbalanced at baseline and

associated with the outcome ($P < .1$) were included in the MMRM model as covariates if both criteria were met.

Analysis of Secondary Outcomes (Specific Aim 3)

This secondary outcome (specific aim 3) tested the hypothesis that infliximab treatment would result in a change in coronary artery *z* worst score of 0.5 or more SDs compared with second IVIG 2 weeks after study treatment, as measured by echocardiography. *z* Worst score was summarized at baseline and study completion. The Haycock equation for body surface area and Dallaire equation for *z* score calculation were applied to the height, weight, and coronary artery dimensions the sites provided.[29,30] The Wilcoxon rank-sum test was performed to compare the *z* worst scores of the 2 treatment groups. A frequency table was provided for the binary *z* worst change by 0.5 or more SD binary score, and Fisher exact test was performed to compare the 2 treatment groups.

Analysis of Exploratory Aim (Specific Aim 4)

We performed a descriptive analysis of symptom burden and symptom persistence by treatment group. We characterized symptom burden as symptom frequency and the average number of symptoms. We defined symptom persistence as the number of days symptoms lasted. Parent observation tool responses were numerically tabulated overall and by study group. Comparisons by study group were evaluated by a 2-sample *t* test.

We used longitudinal clustering techniques (eg, group-based trajectory model) to identify groups of patients with similar progressions in target behavior (eg, the patient's number of symptoms per day) over time by treatment group. These techniques assume that populations are not homogeneous and consist of a limited number of distinct groups. Based on this assumption, these techniques aim to identify closely related data points in a set of data that has no known labels on which to optimize. Specifically, we applied the longitudinal *k* means algorithm, which implements *k* means on longitudinal data, a commonly used longitudinal clustering modeling approach. The *k* means algorithm assumes that the symptom observations of each time point have equal length and are aligned. The symptom observations

are the input of the *k* means clustering algorithm to find the partitioning of symptoms with the minimum within-cluster variance. We specified the number of clusters (*k*) before computing clusters to limit the computational resources needed. We used both the elbow method and the silhouette method for selecting *k*. In the elbow method, the *k* for which within-cluster sum of squares first starts to diminish is shown in the plot of within-cluster sum of squares vs *k* as a visible elbow (https://towardsdatascience.com/clustering-metrics-better-than-the-elbow-method-6926e1f723a6). Because the results of the elbow method may appear ambiguous, we also calculated the silhouette coefficient as $(b - a) / \max(a, b)$, where the mean intracluster distance is *a* and the mean nearest-cluster distance is *b* for each sample.

Changes to the Original Study Protocol

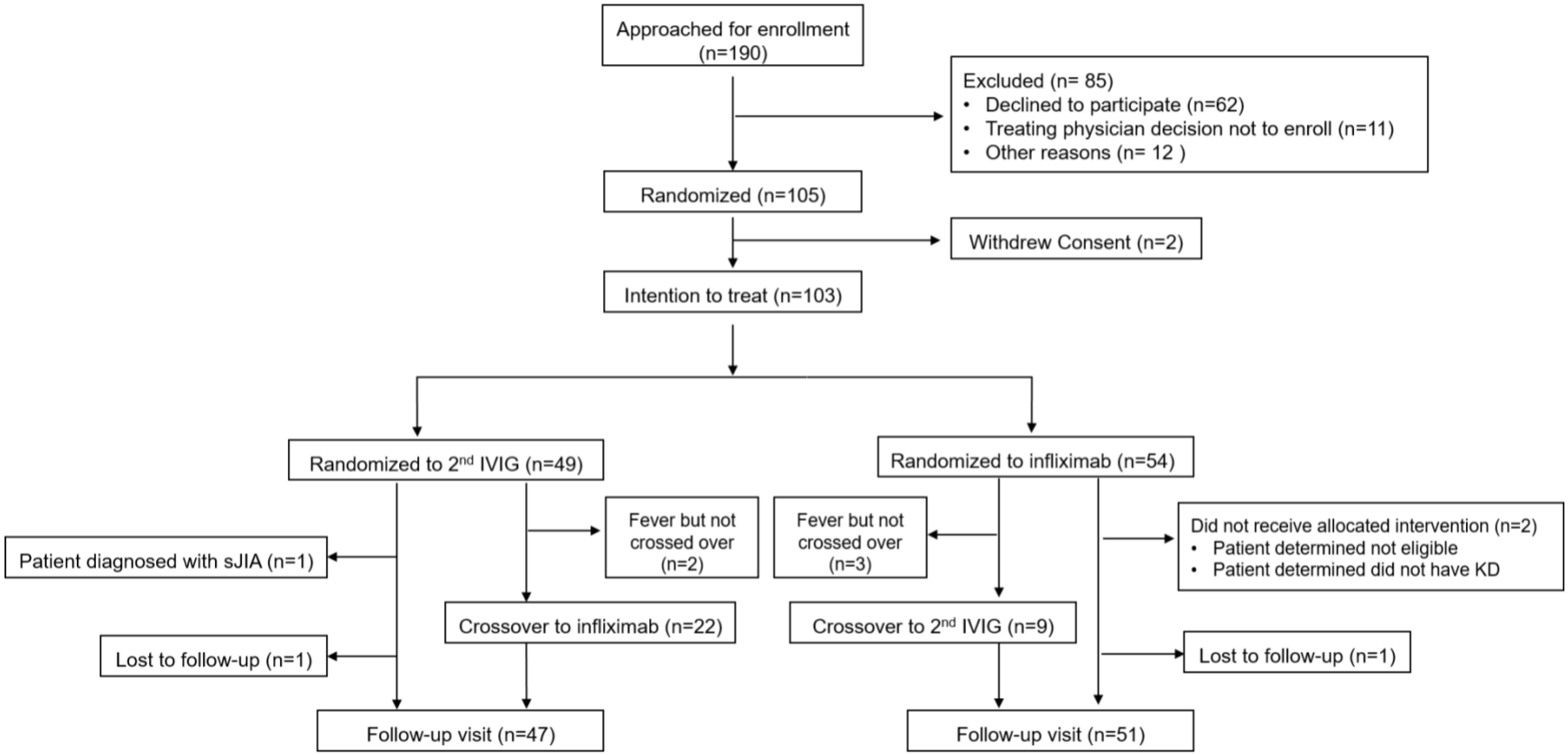
The study period was extended to allow more enrollment, and ultimately the number of participants to be enrolled was decreased from 263 to 112 because of lower-than-expected participant accrual (date protocol change October 4, 2019). In our revised sample size calculations, we assumed that the reference group proportion (ie, second IVIG group) would remain at 67% based on our published clinical trial.[13] The infliximab group proportion was originally assumed to be 82.5% based on a more conservative estimate compared with our published clinical trial (ie, 11 of 12 patients responding). This estimate was changed to an effect size of 89% for infliximab, with a reduced target enrollment of 106 participants. In the revised sample size calculation for the primary end point, we assumed 53 evaluable participants per group (total N = 106) in this 2-group trial to have 80% power to detect a difference between the group proportions of 0.22.

The study was reviewed and approved by the UCSD IRB, and 15 participating sites relied on the UCSD IRB as the IRB of record. All other sites received study approval from their local IRB. All parents and patients signed written consent and assent documents as appropriate.

RESULTS

Over the 3-year study period, 190 patients were approached for participation (Figure 2), and 105 patients were randomly assigned at 22 of the participating institutions (Table 2). After 2 families withdrew consent, 103 participants were included in the ITT analysis. Two more patients randomly assigned to infliximab were removed from the study because 1 had an alternative diagnosis established and the second was determined not to have had a recurrent fever. Comparison of the baseline demographic characteristics of participants who were randomly assigned to infliximab (n = 54) and second IVIG (n = 49) in the ITT analysis showed no significant differences (Table 3). Of the clinical characteristics, only platelet count was significantly different between the treatment groups (*P* = .04) at baseline.

Figure 2. Kawasaki Disease Comparative Effectiveness Consort Flow Diagram



Abbreviations: IVIG, intravenous immunoglobulin; KD, Kawasaki disease; sJIA, systemic onset juvenile idiopathic arthritis.

Table 2. Number of Participants Randomly Assigned by Site

Collaborating organization	Participants,[a] No.
UCSD/Rady Children's Hospital	28
Children's Hospital of Orange County	7
Miller Children's Hospital, Long Beach	6
Harbor-UCLA Medical Center	0
Children's Hospital Los Angeles, Division of Cardiology	0
David Geffen School of Medicine at UCLA	0
Cedars-Sinai Medical Center	0
UCSF Benioff Children's Hospital, Oakland	3
UCSF Benioff Children's Hospital, San Francisco	0
Seattle Children's	3
University of Utah Health Care	6
Children's Hospital Colorado	1
Texas Children's Hospital	1
Children's Health, University of Texas Southwestern Medical Center	6
University of South Dakota, Sanford School of Medicine	0
Children's Mercy, Kansas City	3
Arkansas Children's Hospital	2
Batson Children's Hospital	0
The Ann & Robert H. Lurie Children's Hospital of Chicago	1
The University of Chicago Department of Pediatrics	1
Vanderbilt School of Medicine	1
Emory University School of Medicine	5
Nationwide Children's Hospital	1
Children's National Health System	3
Maria Fareri Children's Hospital at Westchester Medical Center	7
Children's Hospital Boston	1
Indiana University School of Medicine	8
University of Nebraska Medical Center	2
Children's Hospital of Michigan	5
UPMC Children's Hospital of Pittsburgh	0
UAB Children's of Alabama	2

Abbreviations: UCLA, University of California, Los Angeles; UCSD, University of California, San Diego; UCSF, University of California, San Francisco; UPMC, University of Pittsburgh Medical Center; UAB, University of Alabama at Birmingham.

[a]Table includes only participants who did not withdraw consent.

Table 3. Baseline Demographic and Clinical Characteristics of the Study Cohorts

	Infliximab (n = 54)	Second IVIG (n = 49)
Age at enrollment, median (IQR), y	3.6 (2.0-6.4)	2.1 (1.7-5.0)
Age group, No. (%)		
≤1 y >1 y	11 (20) 43 (80)	6 (12) 43 (88)
Illness day at first IVIG treatment, median (IQR)[a]	6.0 (5.0-7.0)	6.0 (5.0-8.0)
Illness day at randomization, median (IQR)	8.0 (7.0-9.8)	9.0 (7.0-11.0)
Incomplete KD, No. (%)	11 (20)	15 (31)
Male, No. (%)	29 (54)	30 (61)
Race, No. (%)		
Asian Black or African American White Other Multiracial Unknown	6 (11) 10 (19) 29 (54) 1 (2) 6 (11) 2 (4)	5 (10) 9 (18) 31 (63) 0 (0) 3 (6) 1 (2)
Hispanic ethnicity, No. (%)	17 (32)	12 (25)
Laboratory data at diagnosis, median (IQR)[b]		
WBC count × 10^9/L	12.8 (8.5-16.7)	13.6 (10.7-19.2)
ANC	8449.0 (5551.5-12 160.9)	9384.0 (6865.5-12 752.5)
*z*Hb	−2.3 (−3.0 to −1.3)	−2.3 (−3.5 to −1.4)
PLT × 10^9/L	324.0 (241.0-398.0)	359.5 (275.8-532.8)
ESR, mm/h	56.5 (41.3-86.3)	68.5 (44.8-89.3)
CRP, mg/dL	14.1 (5.9-20.1)	9.0 (5.1-17.3)
z Worst at baseline, median (IQR)[c]	1.1 (0.7-1.7)	1.4 (0.8-2.1)

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; PLT, platelet count; WBC, white blood cell; *z*Hb, hemoglobin concentration normalized for age.

[a]Illness day 1 = first day of fever.

[b]Sample sizes for baseline laboratory data: ANC infliximab n = 51, second IVIG n = 47; CRP infliximab n = 53, second IVIG baseline n = 48; ESR infliximab n = 52, second IVIG baseline n = 48; PLT infliximab n = 53, second IVIG baseline n = 48; WBC infliximab baseline n = 53, second IVIG n = 49; *z*Hb infliximab n = 53, second IVIG n = 49.

[c]*z* Worst defined as the greatest internal diameter of the right or left anterior descending coronary artery normalized for body surface area; data complete except for 1 missing patient on infliximab.

Primary Outcome (Specific Aim 1)

The primary outcome measure was met by 40 of 52 (77%) and 25 of 49 (51%) participants randomly assigned to infliximab and a second IVIG infusion, respectively (*P* = .0076; OR, 3.2 [95% CI, 1.36-7.52]). Therefore, 12 participants who were randomly assigned to infliximab and 24 participants who were randomly assigned to IVIG had fever more than 24 hours after initiation of their first study treatment. Of these 12 participants randomly assigned to infliximab, 1 participant developed fever 24 hours after the initiation of study treatment but was not crossed over because of hemolytic anemia attributed by the site PI to the initial IVIG treatment (before study entry). The PI declined to give additional IVIG as crossover treatment, and the patient eventually became afebrile without additional therapy. Two additional participants randomly assigned to infliximab developed fever 24 hours after initiation of study treatment but were not crossed over to second IVIG (protocol deviations) and subsequently became afebrile without treatment. Of the 24 participants randomly assigned to second IVIG infusion who had fever more than 24 hours after initiation of their first study treatment, 1 participant was subsequently diagnosed with systemic onset juvenile idiopathic arthritis and 1 participant developed fever 24 hours after initiation of study treatment but was not crossed over to infliximab (protocol deviation) and subsequently became afebrile without treatment. After the initial randomized study treatment, 31 participants crossed over to the other study treatment: 9 participants initially treated with infliximab and 22 participants initially treated with second IVIG. Of the 31 participants who crossed over, 7 of 9 (78%) participants who crossed over to second IVIG infusion and 18 of 22 (82%) who crossed over to infliximab became afebrile after their crossover treatment (*P* > .99). The 6 participants with persistent fever (2 who received infliximab and 4 who received second IVIG as their crossover treatment) were treated with either cyclosporine (n = 1) or steroids (n = 5) at the discretion of the treating physician.

The follow-up visit was standard of care for patients with KD. Although a window of 5 to 18 days was allowed per protocol, all patients were evaluated in a window of 7 to 18 days after

discharge. Two participants did not attend their scheduled standard-of-care KD visit and were lost to follow-up: they could not be contacted despite multiple attempts by clinic staff. Five participants were dropped from the study early for the following reasons: 2 participants' parents withdrew their consent, 1 participant was determined to not have a fever and therefore should not have been enrolled, and 2 were determined to have a different diagnosis (not KD) after enrollment.

Secondary Outcomes (Specific Aim 2)

There was no significant difference between treatment groups in the median values of laboratory measures of inflammation, including WBC count, ANC, and CRP at any time point (baseline, 24 ± 2 hours after completion of the first study treatment, and study completion) (Table 4). Only the median baseline platelet count was significantly higher in participants in the second IVIG group than in the infliximab group (P = .04). Low platelet count may be a marker of disease severity and indicate low-grade disseminated intravascular coagulation. Of the 3 patients with platelet counts under 100 000/μL, 2 were randomly assigned to infliximab and 1 was randomly assigned to second IVIG. The median ESR was significantly higher at study completion in the participants who received a second IVIG infusion (P = .008), which is likely an artifact of higher concentrations of the positively charged Immunoglobulin G molecule that falsely elevates the ESR. At the 24-hour time point, the median hemoglobin concentration normalized for age was significantly lower in the group that received a second IVIG vs infliximab (P = .004). However, by the time of the follow-up visit, there was no significant difference in hemoglobin concentration normalized for age between the groups (P = .13). The change from baseline by treatment and time point was also analyzed for WBC count, ANC, and CRP, and no significant changes were noted in the univariate analysis or in the longitudinal MMRM models. (see Appendix A).

Table 4. Laboratory Measures for Study Participants[a]

	Infliximab (n = 54)	Second IVIG (n = 49)	*P* value[b]
WBC count × 10^9/L, median (IQR)			
Baseline	12.8 (8.5-16.8)	13.6 (10.7-19.2)	.21
24 ± 2 h after completion of tx	13.9 (9.8-16.2)	12.4 (9.2-16.5)	.47
Study completion	9.0 (7.3-11.6)	7.7 (6.5-9.7)	.05
ANC, median (IQR)			
Baseline	8449.0 (5551.5-12 160.9)	9384.0 (6865.5-12 752.5)	.28
24 ± 2 h after completion of tx	5532.1 (3143.3-8753.3)	6120.0 (3694.6-9776.0)	.54
Study completion	3322.5 (1833.0-4555.0)	3133.9 (2040.8-4109.8)	.56
***z*Hb, median (IQR)**			
Baseline	−2.3 (−3.0 to −1.33)	−2.3 (−3.5 to −1.4)	.53
24 ± 2 h after completion of tx	−2.8 (−3.9 to −1.6)	−3.7 (−5.5 to −2.6)	.004
Study completion	−1.9 (−2.6 to −0.5)	−1.8 (−3.5 to −1.1)	.13
PLT × 10^9/L, median (IQR)			
Baseline	324.0 (241.0-398.0)	359.5 (275.8-532.8)	.04
24 ± 2 h after completion of tx	466.0 (361.8-560.3)	511.5 (402.3-690.3)	.06
Study completion	480.0 (390.5-571.0)	490.0 (356.0-583.0)	.87
ESR, mm/h, median (IQR)[b]			
Baseline	56.5 (41.3-86.3)	68.5 (44.8-89.3)	.31
Study completion	48.0 (32.0-62.0)	65.5 (45.0-98.3)	.008
CRP, mg/dL, median (IQR)			
Baseline	14.1 (5.9-20.1)	9.0 (5.1-17.3)	.33
24 ± 2 h after completion of tx	4.9 (2.1-9.3)	3.1 (1.7-8.6)	.37
Study completion	0.5 (0.5-0.7)	0.5 (0.5-0.6)	.59

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PLT, platelet count; tx, treatment; WBC, white blood cell; *z*Hb, hemoglobin concentration normalized for age.

[a]Data were available for the following: ANC infliximab baseline n = 51, 24 h n = 50, study completion n = 46; second IVIG baseline n = 47, 24 h n = 45, study completion n = 43; CRP infliximab baseline n = 53, 24 h n = 51, study completion n = 44; second IVIG baseline n = 48, 24 h n = 47, study completion n = 42; ESR infliximab baseline n = 52, study completion n = 45; second IVIG baseline n = 48, study completion n = 40; PLT infliximab baseline n = 53, 24 h n = 52, study completion n = 47; second IVIG baseline n = 48, 24 h n = 48, study completion n = 45; WBC infliximab baseline n = 53, 24 h n = 52, study completion n = 47; second IVIG baseline n = 49, 24 h n = 48, study completion n = 45; *z*Hb infliximab baseline n = 53, 2 h n = 51, study completion n = 47; second IVIG baseline n = 49, 24 h n = 48, study completion n = 45.

[b]Calculated by Wilcoxon rank-sum test.

[c]Collected only at baseline and study completion.

Site PIs determined that 10 participants had hemolytic anemia based on the following criteria: drop in hemoglobin concentration by at least 2 g/dL at the 24-hour blood draw in conjunction with other supporting laboratory data including a positive direct antibody test,

spherocytes on the peripheral smear, or a decreased haptoglobin level. Of the 58 participants who received IVIG as either their first (n = 49) or second study treatment (n = 9), 9 (15.5%) were determined by the site PI to have developed hemolytic anemia (Table 5A). A 10th participant who received only infliximab as the study treatment had hemolytic anemia that was attributed by the PI to the initial standard-of-care IVIG infusion. An additional 10 participants, 7 of whom received IVIG as their first study treatment and 3 of whom received IVIG as their second study treatment, had at least a 2 g/dL drop in hemoglobin concentration (Table 5B). Thus, a total of 19 of 58 (33%) participants who received IVIG as either their first or second study treatment developed a significant anemia (3 required transfusion) vs only 3 of 43 (7%) participants (none was transfused) who received only infliximab as their study treatment (*P* = .003). Of the 16 participants with at least a 2 g/dL drop in hemoglobin concentration for whom the blood type was known, 10 had blood type A, 3 had blood type B, 1 had blood type AB, and 2 had blood type O. Overall, of the 96 participants for whom the IVIG brand was known, 43 (45%) were treated with the Gammagard brand of IVIG (Takeda Pharmaceuticals), which included 15 of 22 (68%) participants who developed hemolytic anemia. Weight-based dosing of IVIG for obese patients has been reported as a risk factor for hemolytic anemia. However, only 5 of 22 participants who developed presumed hemolytic anemia were classified as overweight or obese based on pediatric criteria from the Centers for Disease Control and Prevention (https://www.cdc.gov/healthyweight/bmi/calculator.html). Of the 3 participants who had a decrease in hemoglobin level of at least 2 g/dL and received only infliximab as their study treatment, 1 was obese and 2 were classified as having a healthy weight.

Table 5. Hemolytic Anemia in Study Participants

Age, y	Sex	Blood type	Baseline Hb	Poststudy tx Hb	Crossover	IVIG brand	Reticulocytes, %	DAT	Comment	Transfused
A. Participants in whom hemolysis after IVIG infusion was recognized										
Participants randomly assigned to IVIG as first study treatment										
1.25	M	A+	9.5	6.8	Yes	Gamunex	3.8	+	HT 362	No
2.0	M	A–	6.8	8.5	No	Gammagard	20.8	–	HT normal	No
2.6	F	A+	11.4	8.2	No	Gammagard	9.9	–	Moderate spherocytes, few schistocytes 3+ Hb in urine	No
2.8	F	B+	11.4	8.6	Yes	Gammagard	5.2	C3-IgG+	HT normal T. bili 1.2	No
3.6	F	A+	12.2	7.3	Yes	Gammagard	10.6	–	T. bili 1.1 Plasma Hb 70 mg/dL	No
6.1	M	AB+	8.5	5.7	No	Gamunex	4.8	3+		Yes
9.3	F	A+	11.3	8.6	Yes	Gammagard	7.0	C3-IgG+	T. bili 1.4	Yes
10.3	M	A+	11.7	9.5	Yes	Gammagard	8.3	–		No
11.0	M	A+	11.2	6.4	No	Gamunex	1.9	3+	T. bili 1.8	Yes
Participants randomly assigned to Infliximab as first study treatment										
7.5	M	A+	10.0	6.7	No	Gammagard	1.2	+	Attributed to first IVIG treatment	No

Age, y	Sex	Blood type	Baseline Hb	Poststudy tx Hb	Crossover	IVIG brand	Reticulocytes, %	DAT	Comment	Transfused
B. Participants who had a ≥2-g drop in Hb concentration over the course of the study but were not specifically evaluated for hemolysis										
Participants randomly assigned to IVIG as first study treatment										
1.1	M	NA	8.8	6.4	No	Gammagard				
2.1	M	NA	11.5	7.8	No	Gamunex-C				
2.9	F	B+	10.6	7.3	No	Gammagard				
2.9	M	O+	9.3	6.7	Yes	Gammagard				
3.0	F	NA	10.3	8.1	Yes	Gammagard				
6.6	M	A+	13.5	6.8	No	Gammagard				
7.4	F	NA	11.7	9.2	Yes	Gamunex				
Participants randomly assigned to infliximab as first study treatment										
4.7	M	NA	11.5	9.1	No	Gammagard				
9.9	M	O+	11.6	8.8	Yes	Gammagard				
10.0	F	A+	10.1	7.6	No	Gammagard				
10.5	M	NA	12.4	8.5	Yes	Gamunex-C				
13.7	F	B+	10.8	7.3	Yes	Gamunex-C				

Abbreviations: DAT, direct antibody test; F, female; Hb, hemoglobin; HT, haptoglobin (normal range 41-165 mg/dL); IVIG, intravenous immunoglobulin; M, male; NA, not available; T. bili, total bilirubin; tx, treatment.

Participants randomly assigned to a second IVIG infusion had a mean (SD) of 2.5 (2.5) fever days from the time of initiation of first study treatment vs 1.5 (1.4) fever days for participants randomly assigned to infliximab (*P* =.014). Hospitalization from the time of study randomization was also longer for patients who were randomly assigned to second IVIG, with a mean (SD) of 4.5 (2.5) days for second IVIG vs 3.2 (2.1) days for infliximab (*P* < .001). This prolongation of hospitalization was related in part to the longer time needed for second IVIG infusion (8-10 hours vs 2 hours for infliximab) and in part to the excess number of patients who needed crossover treatment.

There were 45 AEs in the infliximab group and 65 AEs in the second IVIG group (Table 6). Overall, 24 of 54 (44%) and 33 of 49 (67%) of participants experienced at least 1 AE in the infliximab and second IVIG groups, respectively (*P* = .029). There were a total of 51 SAEs: 15 in the infliximab group and 36 in the second IVIG group. Overall, 37 participants experienced at least 1 SAE: 10 (18%) participants in the infliximab group and 27 (55%) participants in the second IVIG group (*P* < .001). The relationship of AEs to study treatment was adjudicated by the AE committee. None of the participants who received infliximab only and 9 of 58 (15%) participants who received IVIG as either their first or second study treatment experienced SAEs that were deemed definitely or probably related to study treatment. Hemolytic anemia was the SAE for all 9 participants. For the 1 participant in the infliximab group who experienced hemolytic anemia, this SAE was attributed to the first, standard-of-care IVIG infusion and not to the infliximab.

Table 6. Total Adverse Events by Treatment Group[a]

AE, No. (%)	Infliximab 39 AEs[b]	Second IVIG 49 AEs[b]
Fever after 1st randomization	9 (20)	22 (39)
Fever following crossover treatment	2 (5)	3 (6)
Fever after discharge not attributed to Kawasaki disease	8 (19)	3 (6)
Gastrointestinal symptoms	3 (7)	4 (8)
Rash	2 (5)	5 (9)
Epistaxis	2 (5)	3 (6)
Infusion reaction	2 (5)	1 (2)
Arthritis or pain and swelling in extremities	2 (5)	4 (8)
Headache	1 (2)	2 (4)
Upper respiratory infection	1 (2)	2 (4)
Leukemoid reaction	1 (2)	0 (0)
Pancreatitis	1 (2)	0 (0)
Chest pain	1 (2)	0 (0)
Hyperhidrosis	1 (2)	0 (0)
Pain (intravenous site)	1 (2)	0 (0)
Color blindness	1 (2)	0 (0)
Diagnosis of drug reaction with eosinophilia and systemic symptoms due to aspirin or nonsteroidal anti-inflammatory drugs	1 (2)	0 (0)

Abbreviations: AE, adverse event; IVIG, intravenous immunoglobulin.
[a]The 22 participants with presumed hemolytic anemia are summarized in Table 5. Patients with an increase in *z* score ≥0.5 SD are presented in Table 7 and were not included in the AE total numbers.
[b]Of the 45 AEs for the infliximab group, 6 were presumed hemolytic anemia and are described in Table 5. Of the 65 AEs for the second IVIG group, 16 were presumed hemolytic anemia and are described in Table 5.

Secondary Outcomes (Specific Aim 3)

There was no difference in median coronary artery *z* worst score between the groups at baseline or at study completion (Table 7). The AHA guidelines consider a *z* score of 2.5 or higher to be an aneurysm. Overall, 10 of 92 (11%) participants for whom echocardiogram data were available had a *z* worst of 2.5 or higher at study completion. Of these, 4 received infliximab, 1

received second IVIG, and 5 crossed over to receive both treatments (first treatment: IVIG = 3, infliximab = 2). An increase of at least 0.5 SD in the coronary artery *z* worst score from baseline to study completion occurred in 8 (17%) participants who received infliximab as their first study treatment and 3 (7%) participants who received second IVIG (*P* = .197 [95% CI, 0.053-1.524]). At baseline, 1 of 50 (2%) participants randomly assigned to infliximab and 7 of 49 (14%) participants randomly assigned to second IVIG had *z* worst scores of at least 2.5 (*P* = .03). Of the participants with a *z* worst score at baseline less than 2.5, 5 of 47 (11%) participants who received infliximab as their first study treatment and 3 of 45 (7%) participants who received second IVIG progressed to a *z* worst score of at least 2.5 at study completion (*P* = .72). Of the 31 crossover participants, all but 2 had a baseline *z* worst under 2.5, and 5 participants went on to develop aneurysms in 1 or both coronary arteries. One participant in the infliximab group whose baseline *z* worst was 2.86 received no additional treatment and developed a giant aneurysm (*z* worst, 15.01) by the time of study completion.

To explore whether the lower mean platelet count and greater proportion of participants with an initial *z* score of at least 2.5 in the second IVIG group influenced the primary outcome, a sensitivity analysis was performed in which we adjusted for baseline platelet and categorical *z* worst (cutoff of 2.5). These results showed a similar trend for the primary outcome (comparing second IVIG with infliximab: *P* = .0023; OR, 4.3 [95% CI, 1.69-11.17]) as the primary model, which did not adjust for these 2 variables. In addition, a sensitivity analysis was performed with sex (male as the reference group) adjusted in the model as a covariate, which showed no difference in treatment effect.

Table 7. Echocardiographic Data

	Infliximab	Second IVIG	*P* value[a]
z Worst, median (Q1, Q3)[b]			
Baseline	1.13 (0.73, 1.73)	1.37 (0.76, 2.05)	.28
Study completion	1.12 (0.44, 1.68)	1.07 (0.62, 1.42)	.58
z Worst ≥2.5, No. (%)			
Baseline[c]	1 (2)	7 (14)	.03
Study completion	6 (13)	4 (9)	.74
z Worst increase by ≥0.5 SD, No. (%)	8 (18)	3 (7)	.20

Abbreviations: IVIG, intravenous immunoglobulin; Q, quartile.
[a]*P* calculated by Wilcoxon rank-sum test for continuous *z* worst score, Fisher exact test for binary variables.
[b]*z* Worst defined as the maximum internal dimension during the study period of the right or left anterior descending coronary artery normalized for body surface area. *z* Worst data were available for the following: infliximab baseline n = 50, study completion n = 47; second IVIG baseline n = 49, study completion n = 45.
[c]*z* Worst scores at baseline for each participant by treatment group: infliximab, 2.86; 2nd IVIG, 4.49, 4.45, 2.82, 2.8, 2.76, 2.65, 2.53.

Exploratory Aim (Specific Aim 4)

During the study period, which included inpatient stays (baseline and 3 additional observations at 8-hour intervals) and 14 or fewer days after discharge (once per day), 103 participants completed at least 1 symptom report. A total of 6190 individual symptoms were observed and submitted in 1238 reports (a report was recorded as each day a form was submitted).

On average (SD), participants observed 54 (40.47) instances of symptoms over the study period (in hospital and at home). Symptoms were categorized as physical (Figure 3) or behavioral (Figure 4). A symptom report was counted in each period (4 time points in hospital and each day during at home). The mean number of symptoms was calculated from the number of respondents in each setting during the inpatient period, the 14-days-at-home period, and overall, with the denominator including only participants who reported at least once during each period, respectively. This analysis was intended to give an overall ranking of the most common complaints during the observation period. The most common symptom overall was not feeling like one's usual self (mean number of symptom reports per participant = 9.41) and peeling hands or fingers and peeling feet or toes (M = 7.89 and 6.88, respectively). These were

also the most common at home. The most common symptoms in the hospital were rash (M = 3.52), swelling hands (M = 3.28), swelling feet (M = 3.10), and red or bloodshot eyes (M = 3.09).

Figure 3. Physical Symptoms in Hospital, at Home, and Overall

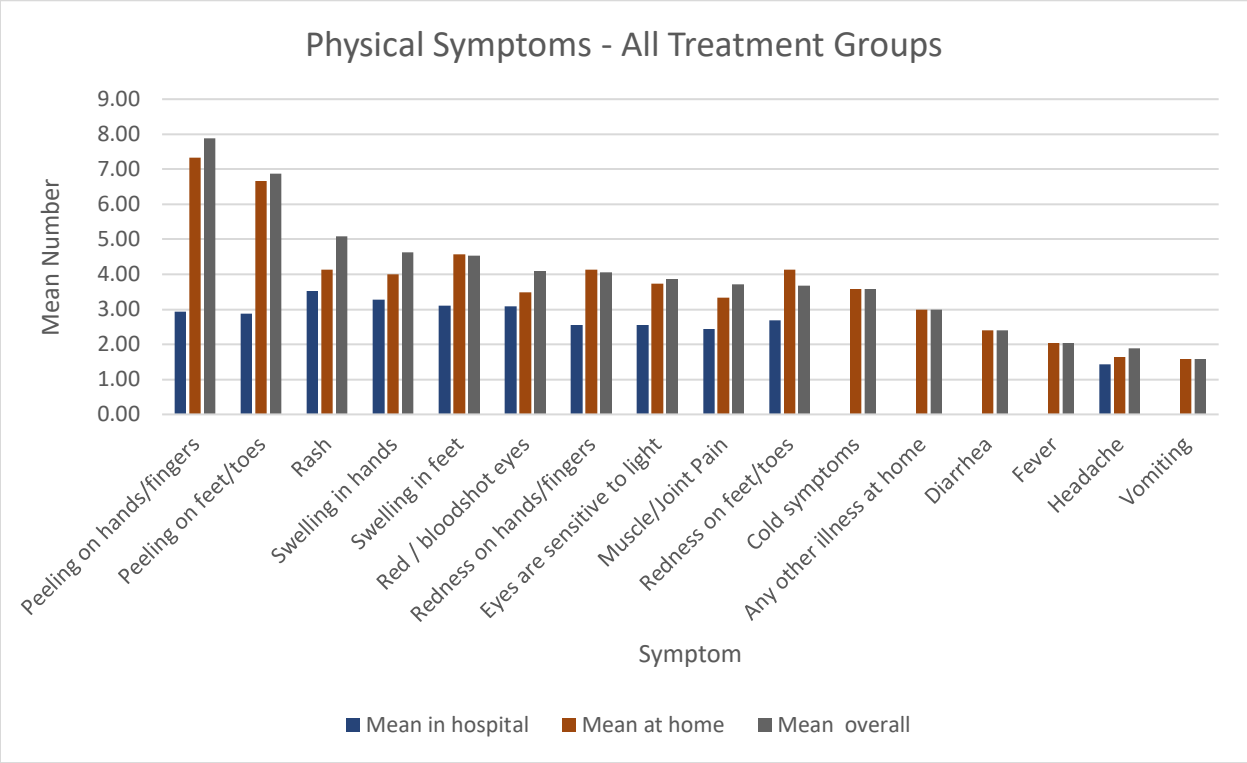
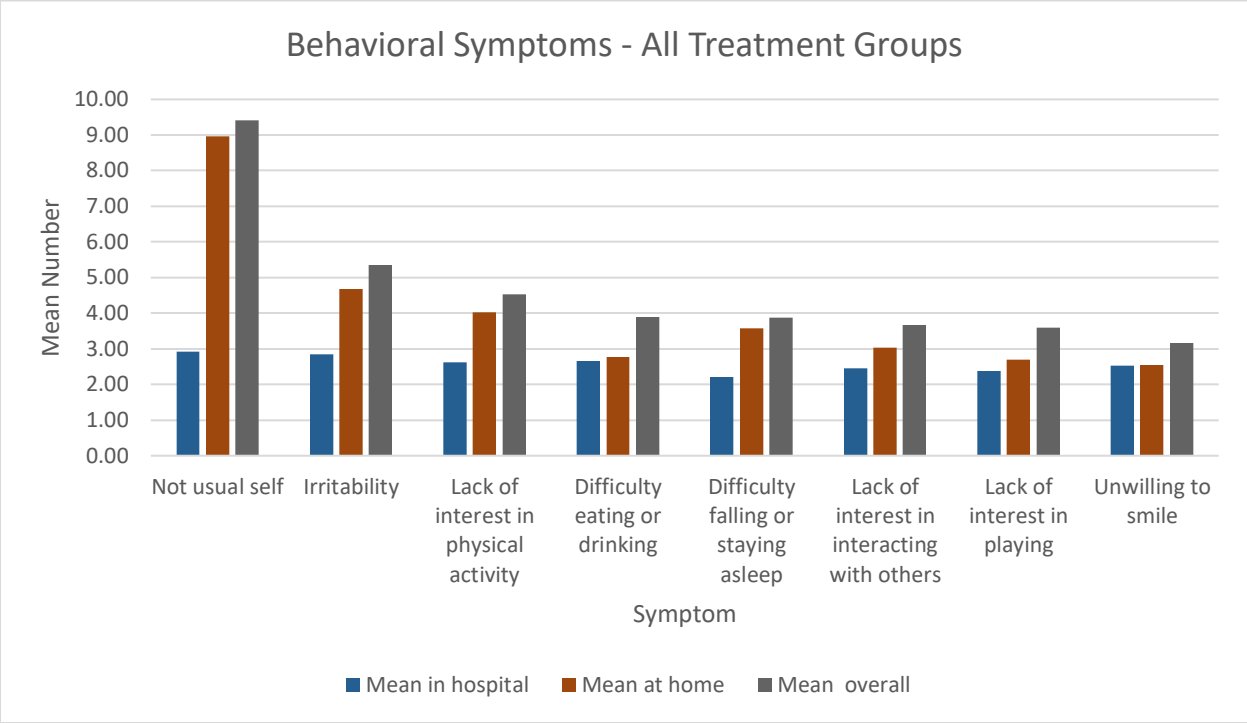


Figure 4. Behavioral Symptoms in Hospital, at Home, and Overall



The symptom burden based on number of symptoms differs by treatment subset (Table 8). The mean number of symptoms was calculated from the number of respondents in each day. The symptom burden was highest for participants who were randomly assigned to infliximab and crossed over to IVIG (subset A2).

Table 8. Breakdown of Symptoms in Hospital and at Home by Treatment Subset

Symptoms	A1 Infliximab[a] n = 43	A2 Crossover to IVIG n = 11	B1 Second IVIG n = 25	B2 Crossover to infliximab n = 24
In hospital, mean, No.	24.28	56.20	24.45	43.77
At home, mean, No.	35.60	65.13	31.06	53.15
Overall, mean, No.	50.38	108.30	48.45	88.09

Abbreviations: IVIG, intravenous immunoglobulin.

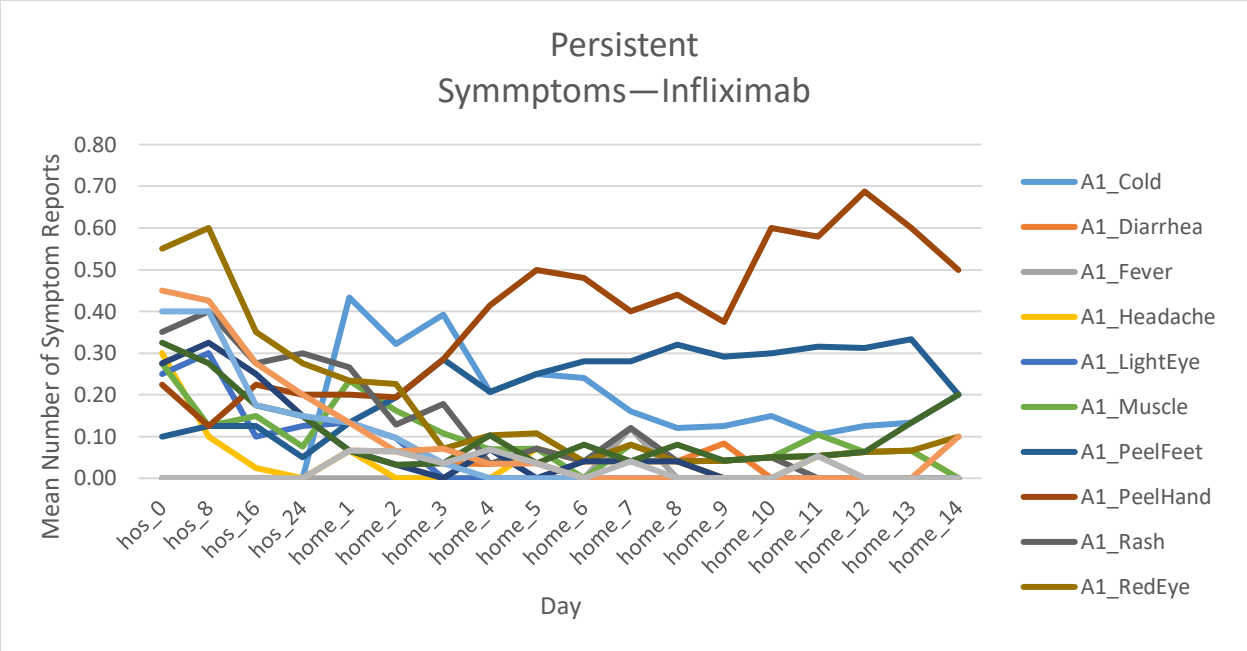
[a]A1 participants were randomly assigned to infliximab, A2 participants were randomly assigned to infliximab and crossed over to 2nd IVIG, B1 participants were randomly assigned to second IVIG, and B2 participants were randomly assigned to 2nd IVIG and crossed over to infliximab.

A 1-way analysis of variance was performed to compare the effects of treatment subsets on total number of symptoms. There was a statistically significant difference in number of symptoms between treatment subsets, with crossover patients (A2 and B2) having a higher number of symptoms reported at each time point compared with noncrossover patients (A1 and B1), $F_{3,99} = 3.96$, $P = .01$.

Symptom Persistence

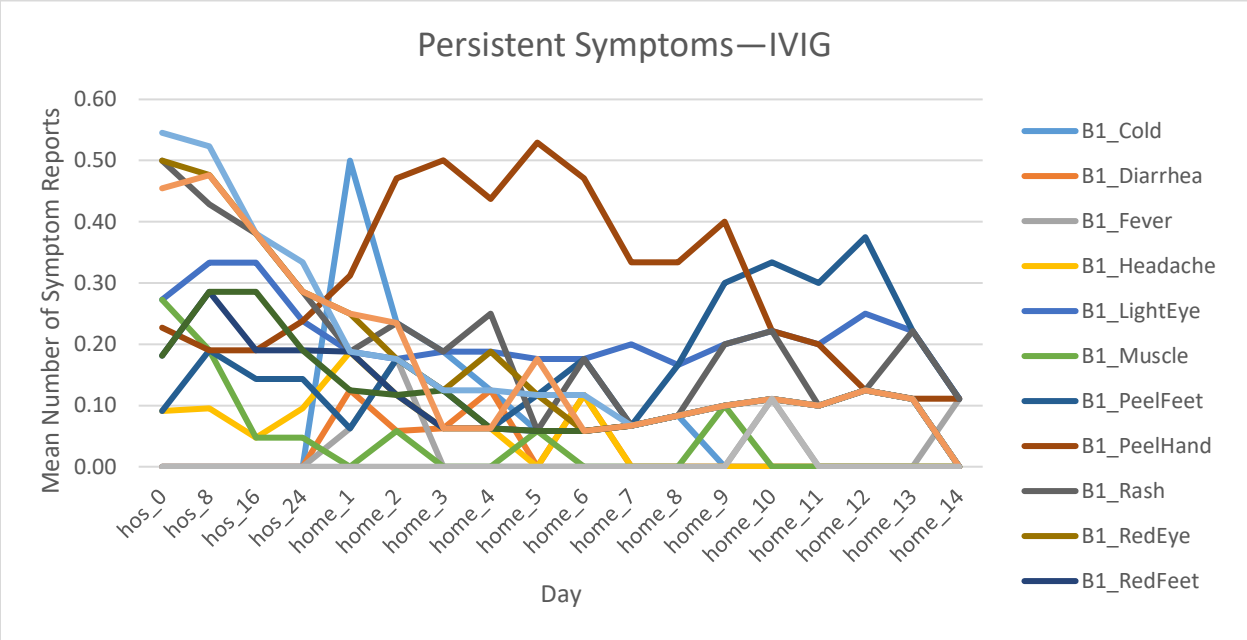
We defined symptom persistence as the number of days symptoms lasted. Four symptoms lasted until day 14 in the infliximab group. The highest mean number of symptom reports among these 4 was peeling hands, followed by peeling feet (Figure 5). There were also 4 symptoms that lasted until day 14 in the IVIG group, all having the same mean number of symptom reports: eyes sensitive to light, peeling hands, peeling feet, and rash (Figure 6). There was 1 persistent symptom in the crossover to IVIG group: peeling hands (Figure 7). Four symptoms lasted until day 14 in the crossover to infliximab group. The highest mean number of symptoms among these 4 was peeling feet, followed by peeling hands (Figure 8).

Figure 5. Persistence of Symptoms in the Infliximab Treatment Group



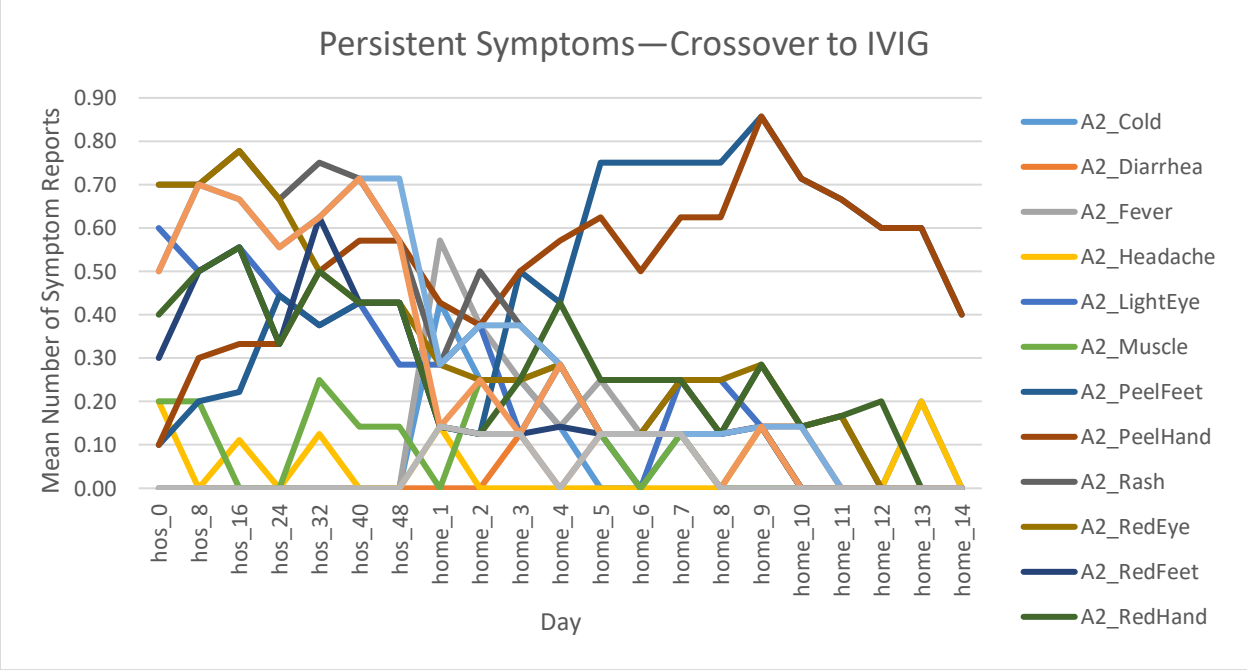
Abbreviations: hos, hospital; LightEye, eyes sensitive to light.

Figure 6. Persistence of Symptoms in the Intravenous immunoglobulin Treatment Group



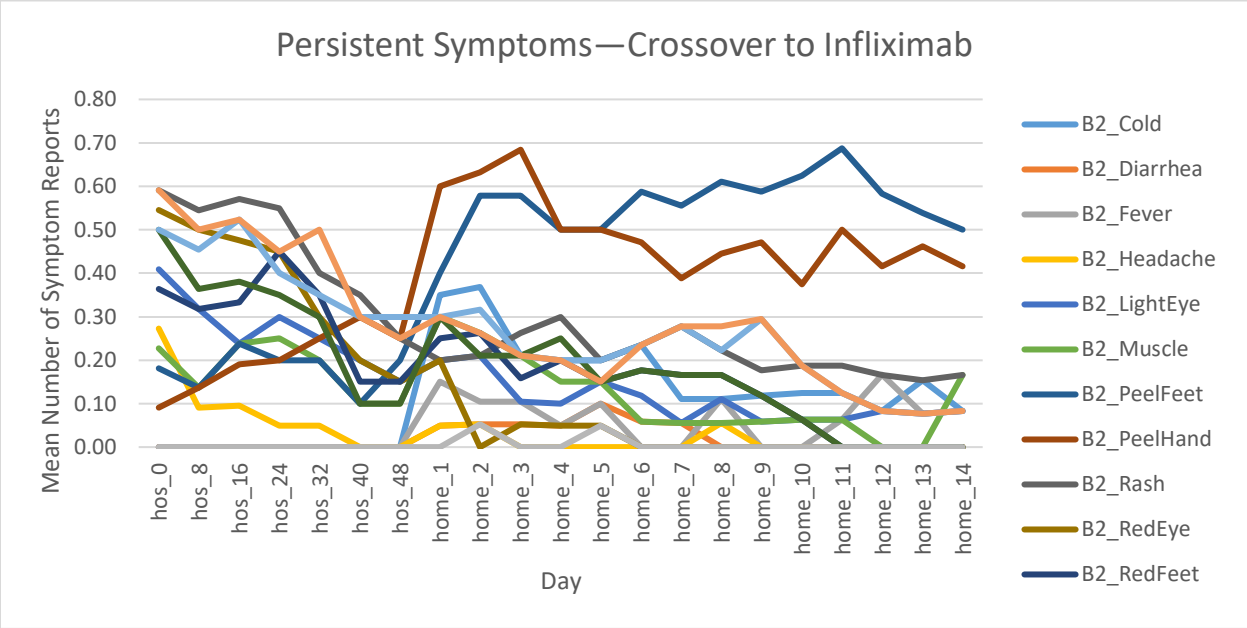
Abbreviations: hos, hospital; LightEye, eyes sensitive to light; IVIG, intravenous immunoglobulin.

Figure 7. Persistence of Symptoms in the Crossover to Intravenous Immunoglobulin Treatment Subset



Abbreviations: hos, hospital; LightEye, eyes sensitive to light; IVIG, intravenous immunoglobulin.

Figure 8. Persistence of Symptoms in the Crossover to Infliximab Treatment Subset



Abbreviations: hos, hospital; LightEye, eyes sensitive to light.

We performed multivariable linear regression analysis to assess whether demographics and clinical characteristics predicted the number of symptoms by treatment group. Independent variables included age, sex, race, ethnicity, the number of days after illness began that the first IVIG infusion was administered, and hemoglobin at 24 hours after admission. Models were run, 1 with total number of symptoms as the dependent variable and 1 with number of physical symptoms. None of the independent variables were significant predictors of the number of symptoms.

DISCUSSION

Summary of Results

The KIDCARE trial compared 2 standard therapies for children with KD and persistent or recrudescent fever 36 hours to 7 days after completion of their initial IVIG infusion. In this comparative effectiveness trial, participants randomly assigned to infliximab had fewer days of fever, less need for additional therapy, less severe anemia, fewer SAEs attributed to study treatment, and shorter hospitalization compared with participants randomly assigned to a second infusion of IVIG. No differences were noted between the 2 treatment groups with respect to resolution of laboratory markers of inflammation or coronary artery outcomes. Specifically, there were no significant differences in CRP, ANC, or worst coronary artery *z* score at any study time point (except baseline) between the treatment groups.

The exploratory analysis of symptoms revealed several interesting results that affected patient experience during treatment and recovery. First, the symptom burden was quite high, with individual patients each experiencing 54 instances of symptoms. The symptom burden appeared to differ by treatment, the highest being the crossover to IVIG. Many patients had symptoms that lasted beyond 14 days; the most persistent was peeling hands or feet. Second, visual inspection of the graphic trajectories of symptoms reveals that all clusters experienced symptoms that decreased over time. However, the IVIG group had a longer period of high symptom burden (ie, many symptoms) compared with the infliximab group: 9 to 10 days vs 4 to 5 days, respectively. Similarly, both crossover groups experienced high symptom burdens longer than that of the infliximab group. Although these are descriptive findings, they offer insights into the different ways patients experience treatment through their symptoms. For example, not feeling like one's usual self may seem nebulous to a clinician, but it was the most common expression of patients' experience.

Heterogeneity of Treatment Effects

The sample size for this trial was too small to yield meaningful results from an analysis of the heterogeneity of treatment effects.

Potential to Affect Health Care Decision-Making

Clinicians who treat patients with KD need guidance for 2 different clinical situations: (1) patients at risk for aneurysms because of elevated *z* scores on the initial echocardiogram and (2) patients with normal initial echocardiograms but persistent fever after the first IVIG infusion. The KIDCARE trial addressed best practice for the latter group. The evidence provided by this comparative effectiveness trial should be considered by all clinicians faced with a patient with KD and IVIG resistance. In order to get widespread adoption of infliximab as the preferred treatment for this patient population, standard guidelines will need to change. The findings in the present study differ from the AHA guidelines, which suggest the use of second IVIG over infliximab or steroids for treatment of IVIG resistance.[1] Similarly, KD treatment guidelines from Japan also recommend a second IVIG infusion as first-line treatment for patients with IVIG-resistant KD.[31] The centers that participated in this trial are leading academic pediatric medical centers in this country. Based on the results of the trial, 17 of the participating centers stated that they would change their practice and adopt infliximab as the first treatment for patients with recurrent fever after the first IVIG infusion.

Clinicians in managed health care settings may also be persuaded to adopt the use of infliximab because of cost issues that were specifically not addressed in the present study but are nonetheless factored into decision-making. The relative cost of infliximab compared with a second IVIG infusion for those with IVIG resistance was the subject of a recent analysis that found a cost savings of $824 759 per 100 patients treated with 10 mg/kg infliximab for IVIG resistance vs second IVIG.[32] The cost savings was driven by lower cost per dose, shorter infusion time, and monitoring for 24 hours before discharge, which resulted in a shorter stay.

Study Limitations

Although this study provides the first adequately powered comparison between 2 treatments for IVIG resistance, we recognize several limitations. There was no centralized interpretation of echocardiograms by a core laboratory, and the assessment of coronary artery changes stratified by treatment must be viewed with that limitation in mind. However, study sites' body surface area and *z* score calculations were standardized by the Data Coordinating

Center. Some sites chose to intensify therapy immediately for patients with an abnormal initial echocardiogram (*z* score ≥2.5) or other high-risk features, so these patients were not enrolled in the study. This decision could have resulted in a selection bias toward inclusion of lower-risk patients. On the other hand, the lower mean platelet count and higher number of participants (n = 7) with a baseline *z* score of at least 2.5 in the second IVIG group could suggest imbalance in disease severity between the groups. However, a sensitivity analysis adjusting for these variables showed a similar trend for the primary outcome.

Although we sought to achieve geographic and racial diversity by including 30 sites nationwide, patient enrollment was not uniform because many sites care for only a limited number of patients with KD each year, and these numbers decreased during the pandemic. A disproportionate number of participants enrolled at the San Diego site, which had a large proportion of Hispanic participants. However, there was no significant difference in the distribution of Hispanic participants between treatment groups. Although hemolytic anemia emerged as a serious side effect of second IVIG infusion, the clinical evaluation of these patients was not complete at all sites, which precluded a detailed description of these events. Furthermore, the study was not designed to determine outcomes beyond the first clinic visit, so data on the effects of therapy that might have occurred beyond this time point were not collected. We also acknowledge that the choice of fevers beyond 24 hours after the first study treatment as the criterion for crossover was arbitrary, and fevers might have resolved spontaneously if a longer time frame had been chosen. For the exploratory aim 4, there was considerable missing data in the reporting of symptoms, which resulted in a lower sample size with limited power. Finally, an open-label study always has the potential to introduce unintentional bias.

Future Research

The result of the KIDCARE trial can be considered pivotal. When the 22 sites that enrolled patients in the trial were polled before and after participation, 2 sites used infliximab as the first re-treatment before and after the trial, and 17 sites stated that they would change their practice and adopt infliximab as the first re-treatment for patients with IVIG-resistant KD.

Three sites that enrolled participants stated that they would continue to use second IVIG because of uncertainty about coronary artery outcomes in the KIDCARE trial. Therefore, the next major trial should study patients with KD who present with an initial abnormal echocardiogram to determine best practice to prevent progression of aneurysms. A multicenter randomized clinical trial is needed to determine the optimal initial treatment intensification for patients with KD who are at high risk of developing CAA based on coronary artery *z* scores on the first echocardiogram. The study should compare infliximab and corticosteroids and abandon a second infusion of IVIG based on the KIDCARE study results, particularly the frequent incidence of hemolytic anemia with the second dose of IVIG and the lower clinical effectiveness of second IVIG. Another productive avenue of research would be to determine the optimal dosage of infliximab in this setting, perhaps with the use of surrogate biomarkers to determine optimal therapeutic response.

CONCLUSIONS

Treatment of patients with IVIG-resistant KD with 10 mg/kg of infliximab resulted in a reduced need for additional therapy, less severe anemia, and shorter hospitalization. However, the study was not powered to assess prevention of coronary artery lesions. No differences were seen between study groups in markers of inflammation, and parents reported similar numbers of symptoms in the 2 treatment groups. Future studies should compare infliximab to methylprednisolone for treatment of IVIG resistance in patients with KD. Until then, infliximab is a safe, well-tolerated, and effective treatment for this patient population that has significant advantages over a second IVIG infusion.

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APPENDICES

Appendix A. MMRM, With and Without Adjustment for Male Sex

APPENDIX A

MMRM with adjustment for male sex

White blood cell count (WBC)

	Infliximab	Second IVIG	Contrast	S.E.	C.I. Lower	C.I. Upper	P-value
24h post completion of tx	0.368 (-1.535,2.27)	-0.515 (-2.494,1.464)	0.883	1.394	-1.867	3.633	0.527
Followup Visit	-3.962 (-5.33,-2.594)	-5.408 (-6.808,-4.008)	1.446	0.994	-0.515	3.407	0.147

Absolute neutrophil count (ANC)

	Infliximab	Second IVIG	Contrast	S.E.	C.I. Lower	C.I. Upper	P-value
24h post completion of tx	-2929.416 (-4530.317,-1328.516)	-2836.814 (-4525.445,-1148.183)	-92.602	1179.591	-2420.75	2235.547	0.938
Followup Visit	-6263.869 (-7213.637,-5314.1)	-6469.161 (-7454.563,-5483.759)	205.292	694.078	-1164.6	1575.187	0.768

C-reactive protein (CRP)

	Infliximab	Second IVIG	Contrast	S.E.	C.I. Lower	C.I. Upper	P-value
24h post completion of tx	-5.424 (-7.629,-3.22)	-7.192 (-9.512,-4.871)	1.767	1.622	-1.434	4.968	0.277
Followup Visit	-12.564 (-13.267,-11.862)	-12.499 (-13.219,-11.778)	-0.066	0.51	-1.073	0.941	0.898

Abbreviations: tx: treatment; S.E.: standard error; C.I.: confidence interval

APPENDIX A

MMRM without adjustment for male sex

White blood cell count (WBC)

	Infliximab	Second IVIG	Contrast	S.E.	C.I. Lower	C.I. Upper	P-value
24h post completion of tx	0.374 (-1.522,2.271)	-0.516 (-2.491,1.458)	0.891	1.39	-1.851	3.632	0.522
Followup Visit	-3.96 (-5.322,-2.598)	-5.414 (-6.806,-4.023)	1.454	0.988	-0.495	3.404	0.143

Absolute neutrophil count (ANC)

	Infliximab	Second IVIG	Contrast	S.E.	C.I. Lower	C.I. Upper	P-value
24h post completion of tx	-2909.173 (-4511.322,-1307.024)	-2837.663 (-4528.225,-1147.102)	-71.51	1180.77	-2401.89	2258.872	0.952
Followup Visit	-6256.953 (-7205.222,-5308.684)	-6499.012 (-7481.03,-5516.995)	242.06	692.029	-1123.74	1607.856	0.727

C-reactive protein (CRP)

	Infliximab	Second IVIG	Contrast	S.E.	C.I. Lower	C.I. Upper	P-value
24h post completion of tx	-5.408 (-7.619,-3.198)	-7.199 (-9.527,-4.872)	1.791	1.627	-1.42	5.001	0.272
Followup Visit	-12.56 (-13.259,-11.861)	-12.517 (-13.233,-11.801)	-0.043	0.507	-1.044	0.958	0.933

Abbreviations: tx: treatment; S.E.: standard error; C.I.: confidence interval

Appendix B. In-Hospital Parent Observation Tool and At-Home Parent Observation Tool

Appendix B

In-Hospital Parent Observation Tool and At Home Parent Observation Tool

KIDCARE:

A Kawasaki Disease Comparative Effectiveness Trial

Study ID _____ Date _____
(To be filled in by study doctor)

Please use this form to record observations about your child during treatment. We ask that you record these observations at four times during the first 24-hour period that your child is in the study:

A. Start of study treatment
B. 8 hours after start of treatment
C. 16 hours after start of treatment
D. 24 hours after start of treatment.

If your child receives an additional study treatment, we ask that you also record for the second 24-hours.

A. 8 hours after start of second treatment
B. 16 hours after start of second treatment
C. 24 hours after start of second treatment.

Before you leave the hospital return this form to _____ (your study doctor).

Study ID _____ Date _____ Time recorded _____ am/pm

A. Start of study treatment.

	At any time from end of first IVIG until start of the current treatment did your child show any of the following signs or symptoms?	**Check ☑ Yes or**	**No**
1	Does your child seem like his/her usual self?	☐	☐
2	Rash	☐	☐
3	Red/bloodshot eyes	☐	☐
4	Eyes are sensitive to light	☐	☐
5	Swelling in hands	☐	☐
6	Redness on hands/fingers	☐	☐
7	Swelling in feet	☐	☐
8	Redness on feet/toes	☐	☐
9	Peeling on hands/fingers	☐	☐
10	Peeling on feet/toes	☐	☐
11	Headache	☐	☐
12	Muscle/Joint Pain	☐	☐
13	Difficulty eating or drinking	☐	☐
14	Unwilling to smile	☐	☐
15	Irritability	☐	☐
16	Lack of interest in playing	☐	☐
17	Lack of interest in physical activity	☐	☐
18	Lack of interest in interacting with others	☐	☐
19	Difficulty falling or staying asleep	☐	☐
20	Describe any other issues you notice such as pain, discomfort, or unusual behaviors that appeared during this period. Any other comments?		

Study ID _____ Date _____ Time recorded _____ am/pm

B. 8 hours after start of study treatment.

	At any time from start of the study treatment did your child show any of the following signs or symptoms?	**Check ☑ Yes or**	**No**
1	Does your child seem like his/her usual self?	☐	☐
2	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
3	Red/bloodshot eyes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Swelling in hands	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
6	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Swelling in feet	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Peeling on hands/fingers	☐	☐
10	Peeling on feet/toes	☐	☐
11	Headache	☐	☐
12	Muscle/Joint Pain	☐	☐
13	Difficulty eating or drinking	☐	☐
14	Unwilling to smile	☐	☐
15	Irritability	☐	☐
16	Lack of interest in playing	☐	☐
17	Lack of interest in physical activity	☐	☐
18	Lack of interest in interacting with others	☐	☐
19	Difficulty falling or staying asleep	☐	☐
20	Describe any other issues you notice such as pain, discomfort, or unusual behaviors that appeared during this period. Any other comments?		

Study ID _____ Date _____ Time recorded _____ am/pm

C. 16 hours after start of study treatment.

	At any time within 8 to 16 hours since the start of the study treatment, did your child show the following signs or symptoms?	**Check ☑ Yes or**	**No**
1	Does your child seem like his/her usual self?	☐	☐
2	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
3	Red/bloodshot eyes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Swelling in hands	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
6	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Swelling in feet	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Peeling on hands/fingers	☐	☐
10	Peeling on feet/toes	☐	☐
11	Headache	☐	☐
12	Muscle/Joint Pain	☐	☐
13	Difficulty eating or drinking	☐	☐
14	Unwilling to smile	☐	☐
15	Irritability	☐	☐
16	Lack of interest in playing	☐	☐
17	Lack of interest in physical activity	☐	☐
18	Lack of interest in interacting with others	☐	☐

19	Difficulty falling or staying asleep	☐	☐
20	Describe any other issues you notice such as pain, discomfort, or unusual behaviors that appeared during this period. Any other comments?		

Study ID _____ Date _____ Time recorded _____ am/pm

D. 24 hours after start of study treatment.

	At any time within 16 to 24 hours since the start of the study treatment, did your child show the following signs or symptoms?	**Check ☑ Yes or**	**No**
1	Does your child seem like his/her usual self?	☐	☐
2	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
3	Red/bloodshot eyes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Swelling in hands	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
6	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Swelling in feet	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Peeling on hands/fingers	☐	☐
10	Peeling on feet/toes	☐	☐
11	Headache	☐	☐
12	Muscle/Joint Pain	☐	☐
13	Difficulty eating or drinking	☐	☐
14	Unwilling to smile	☐	☐

15	Irritability	☐	☐
16	Lack of interest in playing	☐	☐
17	Lack of interest in physical activity	☐	☐
18	Lack of interest in interacting with others	☐	☐
19	Difficulty falling or staying asleep	☐	☐
20	Describe any other issues you notice such as pain, discomfort, or unusual behaviors that appeared during this period. Any other comments?		

E. Parent Home Observation Tool- <u>Information for Coordinator</u>

- **Please have the parent choose which method (email or paper) they would like to complete the daily home observation tool for 2 weeks, and have parents fill out the attached form in packet (form A).**
- **If the parent chooses <u>e-mail</u> method please call: 510-761-5406 and leave a message with:**
  - **Your name and phone number with area code**
  - **Subject ID number**
  - **Date of the subject's follow-up visit**
  - **Parent's e-mail address spelled out**
- **If parent choose paper:**
  - **Provide them with all 14 copies of the parent home observation tool in packet**
  - **Prefill in their subject ID on each page and dates of anticipated completion if possible**
  - **Staple/clip packet of surveys together with parent instruction page on top**

Method of KIDCARE Parent Observation Home Tool Completion (form A)

Study ID _____ Date _____

You will record whether your child is experiencing certain symptoms associated with the illness at home. You will respond either by email or on paper daily during the next two weeks. This will start after your child leaves the hospital. You will be provided an example of the survey. ***Please note: answering these questionnaires are not a substitute for communication with your study doctor. Please contact your study doctor with any questions or concerns about your child's health or participation in this study.***

I prefer to complete these daily questions:

- ☐ Online with contact by email
  My email address is _____
  (The survey email will come from kathykim@ucdavis.edu.)

- ☐ On paper.
  Your study coordinator will give you instructions and paper copies. Please return at your follow up visit.

Parent Home Observation Tool- <u>Instructions for Parent</u>

Thank you for participating in our study. Attached you will find 14 copies of the home observation symptom questionnaire. You will start filling out the survey after your child leaves the hospital, or on the third day of their hospital stay. Please fill out one questionnaire around the same time daily. You will answer the questions based on your child's symptoms over a 24 hour time period.

On the top of every questionnaire, please write down the date and time you completed the questionnaire. Please bring the packet of completed questionnaires with you to your child's follow-up visit. There may be some questionnaires not completed based on your child's follow-up visit date. ***Please note: answering these questionnaires are not a substitute for communication with your study doctor. Please contact your study doctor with any questions or concerns about your child's health or participation in this study.***

Day 1: Study ID _____ Date _____ Time recorded _____ am/pm

	At any time in the last 24 hours did your child show the following symptoms?	Check Yes or ☑	No
1	Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2	Does your child seem like his/her usual self?	☐	☐
3	Rash If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
4	Red/bloodshot eyes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
5	Eyes are sensitive to light If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
6	Swelling in hands If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
7	Redness on hands/fingers If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
8	Swelling in feet If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
9	Redness on feet/toes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐

22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 2: Study ID _____ Date _____ Time recorded _____ am/pm

	At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or**	**No**
1	Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2	Does your child seem like his/her usual self?	☐	☐
3	Rash If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
4	Red/bloodshot eyes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
5	Eyes are sensitive to light If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
6	Swelling in hands If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
7	Redness on hands/fingers If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
8	Swelling in feet If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
9	Redness on feet/toes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐

17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 3: Study ID _____ Date _____ Time recorded _____ am/pm

	At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or**	**No**
1	Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2	Does your child seem like his/her usual self?	☐	☐
3	Rash If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
4	Red/bloodshot eyes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
5	Eyes are sensitive to light If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
6	Swelling in hands If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
7	Redness on hands/fingers If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
8	Swelling in feet If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
9	Redness on feet/toes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐

12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 4: Study ID _____ Date _____ Time recorded _____ am/pm

	At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or**	**No**
1	Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2	Does your child seem like his/her usual self?	☐	☐
3	Rash If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
4	Red/bloodshot eyes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
5	Eyes are sensitive to light If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
6	Swelling in hands If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
7	Redness on hands/fingers If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
8	Swelling in feet	☐	☐

	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 5: Study ID _____ Date _____ Time recorded _____ am/pm

At any time in the last 24 hours did your child show the following symptoms?		**Check ☑ Yes or**	**No**
1	Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2	Does your child seem like his/her usual self?	☐	☐
3	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Red/bloodshot eyes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		

6	Swelling in hands If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
7	Redness on hands/fingers If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
8	Swelling in feet If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
9	Redness on feet/toes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 6: Study ID _____ Date _____ Time recorded _____ am/pm

At any time in the last 24 hours did your child show the following symptoms?		**Check ☑ Yes or No**	
1	Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2	Does your child seem like his/her usual self?	☐	☐
3	Rash If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐

4	Red/bloodshot eyes				☐	☐
	If Yes: Compared to 8 hours ago it is	☐ Better	☐ Same	☐ Worse		
5	Eyes are sensitive to light				☐	☐
	If Yes: Compared to 8 hours ago it is	☐ Better	☐ Same	☐ Worse		
6	Swelling in hands				☐	☐
	If Yes: Compared to 8 hours ago it is	☐ Better	☐ Same	☐ Worse		
7	Redness on hands/fingers				☐	☐
	If Yes: Compared to 8 hours ago it is	☐ Better	☐ Same	☐ Worse		
8	Swelling in feet				☐	☐
	If Yes: Compared to 8 hours ago it is	☐ Better	☐ Same	☐ Worse		
9	Redness on feet/toes				☐	☐
	If Yes: Compared to 8 hours ago it is	☐ Better	☐ Same	☐ Worse		
10	Peeling on hands/fingers				☐	☐
11	Peeling on feet/toes				☐	☐
12	Headache				☐	☐
13	Muscle/Joint Pain				☐	☐
14	Difficulty eating or drinking				☐	☐
15	Unwilling to smile				☐	☐
16	Irritability				☐	☐
17	Lack of interest in playing				☐	☐
18	Lack of interest in physical activity				☐	☐
19	Lack of interest in interacting with others				☐	☐
20	Difficulty falling or staying asleep				☐	☐
21	Cold symptoms (runny nose, cough, sore throat)				☐	☐
22	Vomiting				☐	☐
23	Diarrhea				☐	☐
24	Any other illnesses				☐	☐

Day 7: Study ID _____ Date _____ Time recorded _____ am/pm

At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or No**

1 Fever (temperature above 38° C or 100.4° F) ☐ ☐

How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)

2 Does your child seem like his/her usual self? ☐ ☐

3 Rash

If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse

4 Red/bloodshot eyes ☐ ☐

If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse

5 Eyes are sensitive to light ☐ ☐

If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse

6 Swelling in hands ☐ ☐

If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse

7 Redness on hands/fingers ☐ ☐

If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse

8 Swelling in feet ☐ ☐

If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse

9 Redness on feet/toes ☐ ☐

If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse

10 Peeling on hands/fingers ☐ ☐

11 Peeling on feet/toes ☐ ☐

12 Headache ☐ ☐

13 Muscle/Joint Pain ☐ ☐

14 Difficulty eating or drinking ☐ ☐

15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 8: Study ID _____ Date _____ Time recorded _____ am/pm

	At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or**	**No**
1	Fever (temperature above 38° C or 100.4° F)	☐	☐
	How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)		
2	Does your child seem like his/her usual self?	☐	☐
3	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Red/bloodshot eyes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		

6	Swelling in hands	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Swelling in feet	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 9: Study ID _____ Date _____ Time recorded _____ am/pm

	At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes**	**or No**
1	Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2	Does your child seem like his/her usual self?	☐	☐
3	Rash If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
4	Red/bloodshot eyes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
5	Eyes are sensitive to light If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
6	Swelling in hands If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
7	Redness on hands/fingers If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
8	Swelling in feet If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
9	Redness on feet/toes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
10	Peeling on hands/fingers	☐	☐

11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 10: Study ID _____ Date _____ Time recorded _____ am/pm

	At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or**	**No**
1	Fever (temperature above 38° C or 100.4° F)	☐	☐
	How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)		
2	Does your child seem like his/her usual self?	☐	☐
3	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		

4	Red/bloodshot eyes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
6	Swelling in hands	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Swelling in feet	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐

20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 11: Study ID _____ Date _____ Time recorded _____ am/pm

At any time in the last 24 hours did your child show the following symptoms?		**Check ☑ Yes or**	**No**
1	Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2	Does your child seem like his/her usual self?	☐	☐
3	Rash If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
4	Red/bloodshot eyes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
5	Eyes are sensitive to light If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
6	Swelling in hands If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
7	Redness on hands/fingers If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐

8	Swelling in feet	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 12: Study ID _____ Date _____ Time recorded _____ am/pm

At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or No**

1	Fever (temperature above 38° C or 100.4° F)	☐	☐
	How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)		
2	Does your child seem like his/her usual self?	☐	☐
3	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Red/bloodshot eyes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
6	Swelling in hands	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Swelling in feet	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐

15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 13: Study ID _____ Date _____ Time recorded _____ am/pm

	At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or**	**No**
1	Fever (temperature above 38° C or 100.4° F)	☐	☐
	How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)		
2	Does your child seem like his/her usual self?	☐	☐
3	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Red/bloodshot eyes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		

6	Swelling in hands	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Swelling in feet	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Day 14: Study ID _____ Date _____ Time recorded _____ am/pm

At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or No**	
1 Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2 Does your child seem like his/her usual self?	☐	☐
3 Rash If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
4 Red/bloodshot eyes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
5 Eyes are sensitive to light If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
6 Swelling in hands If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
7 Redness on hands/fingers If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
8 Swelling in feet If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
9 Redness on feet/toes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐

10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

Appendix C. Site and PI Information

Site No.	Collaborating Organization	PI	Address	City, State Zip	E-mail
01	**University of California San Diego/Rady Children's Hospital**	**Jane Burns** **Adriana Tremoulet**	**3020 Children's Way**	**San Diego, Ca 92123**	jcburns@ucsd.edu atremoulet@ucsd.edu
02	University of Hawaii, Kapi'olani Medical Specialists	Marian Melish	1319 Punahou Street, Suite 1160	Honolulu, HI 96822	mmelish@hawaii.edu
03	Children's Hospital of Orange County	Negar Ashouri	455 South Main	Orange, CA 92868	nashouri@choc.org
04	Miller Children's Hospital, Long Beach	David Michalik	2801 Atlantic Avenue, P.O. Box 1428	Long Beach, CA 90801-1428	DMichalik@memorialcare.org
05	Harbor-UCLA Medical Center	Sylvia Yeh	1000 W. Carson Street	Torrance, CA 90502	syeh@uclacvr.labiomed.org
06	Children's Hospital Los Angeles, Division of Cardiology	Jackie Szmuszkovicz Michal Cidon	4650 Sunset Blvd	Los Angeles, CA 90027	JSzmuszkovicz@chla.usc.edu mcidon@chla.usc.edu
07	David Geffen School of Medicine at UCLA	Yvonne Bryson Nancy Halnon Paul Krogstad	10833 Le Conte Avenue	Los Angeles, CA 90095	ybryson@mednet.ucla.edu nhalnon@mednet.ucla.edu pkrogstad@mednet.ucla.edu
08	Cedars-Sinai Medical Center	Moshe Arditi	8700 Beverly Blvd	West Hollywood, CA 90048	Moshe.Arditi@cshs.org
09	Stanford School of Medicine	Cornelia Dekker	300 Pasteur Drive, Room G312	Stanford, CA 94305	cdekker@stanford.edu
10	UCSF Benioff Children's Hospital	Gregory Kurio Michele Long	747 52nd Street, 2nd Floor	Oakland, CA 94609	gkurio@mail.cho.org Michele.Long@ucsf.edu
11	UC Davis Children's Hospital	Natasha Nakra	2516 Stockton Blvd., TICON II	Sacramento, CA 95817	nnakra@ucdavis.edu
12	Seattle Children's	Michael Portman	1900 Ninth Avenue	Seattle, WA 98101-1309	michael.portman@seattlechildrens.org
13	University of Utah Health Care	Lloyd Tani Dongngan Truong	81 N. Mario Capecchi Drive	Salt Lake City, UT 84113	lloyd.tani@hsc.utah.edu Dongngan.truong@hsc.utah.edu
14	Children's Hospital Colorado	Pei-Ni Jone	13123 East 16th Avenue	Aurora, CO 80045	Pei-Ni.Jone@childrenscolorado.org
15	Texas Children's Hospital	S. Kristen Sexson Tejtel	6621 Fannin, Suite 19345-C	Houston, TX 77030	sxsexson@texaschildrens.org
16	Children's Health, University of Texas Southwestern Medical Center	Kavita Sharma, M.D.	1935 Medical District Drive	Dallas, TX 75235	Kavita.Sharma@UTSouthwestern.edu
17	University of South Dakota, Sanford School of Medicine	Archana Chatterjee	1400 West 22nd Street	Sioux Falls, SD 57105-1570	Archana.Chatterjee@SanfordHealth.org
18	Children's Mercy, Kansas City	Mary Anne Jackson	2401 Gillham Road	Kansas City, MO 64108	mjackson@cmh.edu
19	Arkansas Children's Hospital	Jose Romero	1 Children's Way	Little Rock, AR 72202-3591	RomeroJose@uams.edu
20	Children's of Mississippi	Rana El Feghaly	2500 North State Street	Jackson, MI 39216	relfeghaly@umc.edu
21	Northwestern Memorial Hosp, Northwestern University, Chicago, IL	Anne Rowley	251 East Huron Street	Chicago, IL 60611	a-rowley@northwestern.edu
22	The University of Chicago Department of Pediatrics	Robert Daum	5841 South Maryland Avenue, MC 6054	Chicago, IL 60637-1470	rdaum@bsd.uchicago.edu
23	Vanderbilt School of Medicine	Natasha Halasa	2200 Children's Way	Nashville, TN 37232	natasha.halasa@Vanderbilt.Edu
24	Emory University School of Medicine	David Lloyd	1405 Clifton Road NE	Atlanta, GA 30322	David.Lloyd@choa.org
25	Nationwide Children's Hospital	Preeti Jaggi	700 Children's Drive	Columbus, OH 43205	Preeti.Jaggi@nationwidechildrens.org
26	Children's National Health System	Roberta DeBiasi	111 Michigan Avenue, NW	Washington, DC 20010-2970	RDebiasi@childrensnational.org
27	The Children's Hospital of Philadelphia	Edward M. Behrens, M.D.	3615 Civic Center Blvd, 1102 Abramson Research Center	Philadelphia, PA 19104-4399	behrens@email.chop.edu
28	Maria Fareri Children's Hospital at Westchester Medical Center	Supriya Jain, M.D.	40 Sunshine Cottage Road	Valhalla, NY 10595	Supriya_Jain@bchphysicians.org
29	Children's Hospital Boston	Jane Newburger	300 Longwood Avenue	Boston, MA 02115	Jane.Newburger@CARDIO.CHBOSTON.ORG
	Partners				
	UC Davis	Katherine Kim			kathykim@ucdavis.edu
	patient/parent co-investigators	Katie Rauschl			katierauschl@me.com
	patient/parent co-investigators	Anna Lillian			alillian21@gmail.com

KIDCARE (PCORI) SITE MASTER LIST, 2/15/17

Site No.	Collaborating Organization	Address	City	State	Zip
01	**University of California San Diego/Rady Children's Hospital**	**3020 Children's Way**	**San Diego**	CA	92123
02	University of Hawaii, Kapi'olani Medical Specialists	1319 Punahou Street, Suite 1160	Honolulu	HI	96822
03	Children's Hospital of Orange County	455 South Main	Orange	CA	92868
04	Miller Children's Hospital, Long Beach	2801 Atlantic Avenue, P.O. Box 1428	Long Beach	CA	90801
05	Harbor-UCLA Medical Center	1000 W. Carson Street	Torrance	CA	90502
06	Children's Hospital Los Angeles, Division of Cardiology	4650 Sunset Blvd	Los Angeles	CA	90027
07	David Geffen School of Medicine at UCLA	10833 Le Conte Avenue	Los Angeles	CA	90095
08	Cedars-Sinai Medical Center	8700 Beverly Blvd	West Hollywood	CA	90048
09	Stanford School of Medicine	300 Pasteur Drive, Room G312	Stanford	CA	94305
10	UCSF Benioff Children's Hospital	747 52nd Street, 2nd Floor	Oakland	CA	94609
11	UC Davis Children's Hospital	2516 Stockton Blvd., TICON II	Sacramento	CA	95817
12	Seattle Children's	1900 Ninth Avenue	Seattle	WA	98101
13	University of Utah Health Care	81 N. Mario Capecchi Drive	Salt Lake City	UT	84113
14	Children's Hospital Colorado	13123 East 16th Avenue	Aurora	CO	80045
15	Texas Children's Hospital	6621 Fannin, Suite 19345-C	Houston	TX	77030
16	Children's Health, University of Texas Southwestern Medical Center	1935 Medical District Drive	Dallas	TX	75235
17	University of South Dakota, Sanford School of Medicine	1400 West 22nd Street	Sioux Falls	SD	57105
18	Children's Mercy, Kansas City	2401 Gillham Road	Kansas City	MO	64108
19	Arkansas Children's Hospital	1 Children's Way	Little Rock	AR	72202
20	Children's of Mississippi	2500 North State Street	Jackson	MS	39216
21	Northwestern Memorial Hosp, Northwestern University, Chicago, IL	251 East Huron Street	Chicago	IL	60611
22	The University of Chicago Department of Pediatrics	5841 South Maryland Avenue, MC 6054	Chicago	IL	60637
23	Vanderbilt School of Medicine	2200 Children's Way	Nashville	TN	37212
24	Emory University School of Medicine	1405 Clifton Road NE	Atlanta	GA	30322
25	Nationwide Children's Hospital	700 Children's Drive	Columbus	OH	43205
26	Children's National Health System	111 Michigan Avenue, NW	Washington	DC	20010
27	The Children’s Hospital of Philadelphia	3615 Civic Center Blvd, 1102 Abramson Research Center	Philadelphia	PA	19104
28	Maria Fareri Children's Hospital at Westchester Medical Center	40 Sunshine Cottage Road	Valhalla	NY	10595
29	Children's Hospital Boston	300 Longwood Avenue	Boston	MA	02115

Disclaimer:
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