Long-term treatment with romiplostim and treatment-free platelet responses in children with chronic immune thrombocytopenia

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Supplementary Data

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| Condition                               | n (%) |
|----------------------------------------|-------|
| Thrombocytopenia                        | 4 (6) |
| Pyrexia                                 | 3 (5) |
| Epistaxis                               | 2 (3) |
| Headache                                | 2 (3) |
| Vomiting                                | 2 (3) |
| Anemia                                  | 1 (2) |
| Asthenia                                | 1 (2) |
| Asthma                                  | 1 (2) |
| Biliary dyskinesia                      | 1 (2) |
| *Clostridium difficile* infection       | 1 (2) |
| Contusion                               | 1 (2) |
| Dehydration                             | 1 (2) |
| Depression                              | 1 (2) |
| Febrile neutropenia                     | 1 (2) |
| Gastroenteritis                         | 1 (2) |
| Gastrointestinal infection              | 1 (2) |
| Gingivitis                              | 1 (2) |
| Hemangiomia                             | 1 (2) |
| Hematoma                                | 1 (2) |
| Head injury                             | 1 (2) |
| Immune thrombocytopenia                 | 1 (2) |
| Infection                               | 1 (2) |
| Leukopenia                              | 1 (2) |
| Meningitis viral                        | 1 (2) |
| Metapneumovirus infection               | 1 (2) |
| Mouth hemorrhage                        | 1 (2) |
| Pharyngitis streptococcal               | 1 (2) |
| Platelet count decreased                | 1 (2) |
| Pneumonia mycoplasmal                   | 1 (2) |
| Post-procedural hemorrhage              | 1 (2) |
| Respiratory syncytial virus infection   | 1 (2) |
| Subcutaneous abscess                    | 1 (2) |
| Suicidal ideation                       | 1 (2) |
| Transfusion reaction                    | 1 (2) |
| Ulcer hemorrhage                        | 1 (2) |
| Viral infection                         | 1 (2) |
| Viral upper respiratory tract infection | 1 (2) |
Table S2. Serious and/or grade 3 bleeding adverse events.

| Age (years) | Sex | Week | Bleeding adverse events                                      | Duration (days) | Grade | Related | Serious | Actions                                                                 |
|------------|-----|------|---------------------------------------------------------------|-----------------|-------|---------|---------|-------------------------------------------------------------------------|
| 7          | Boy * | 95   | Hematoma                                                      | 16              | 1     | N       | Y       | Hospitalized, no change to romiplostim                                  |
| 4          | Boy  | 24   | Epistaxis and mouth hemorrhage                                | 1               | 2     | N       | Y       | Hospitalized, no change to romiplostim                                  |
| 11         | Girl | 40   | Worsening ITP and contusion                                   | 3               | 1     | N       | Y       | Hospitalized, left the study a few days later for noncompliance         |
| 7          | Boy  | 12   | Worsening epistaxis, concurrent grade 4 thrombocytopenia      | 2               | 3     | Y       | Y       | Hospitalized, no change to romiplostim (later D/C as req other Rx)     |
| 3          | Girl | 3    | Bleeding mouth sores                                          | 1               | 3     | N       | Y       | ER                                                                      |
| 14         | Boy  | 294  | Hematuria                                                     | 5               | 3     | N       | N       | ER, no change to romiplostim                                            |
| 8          | Boy  | 94   | Increased petechiae                                           | 13              | 3     | N       | N       | No change to romiplostim (later D/C as req other Rx)                    |

D/C: discontinued; ER: emergency room; ITP: immune thrombocytopenia; N: no; req: required; Rx: therapy; Y: yes.

*This patient reported 499 adverse events.
## Table S3. Rescue medications.

|                        | All treated patients (N=65) |
|------------------------|-----------------------------|
|                        | n (%) | Events (rate per 100 pt-yr) |
| Any use                | 23 (35) | 80 (44) |
| Intravenous immunoglobulin | 11 (17) | 31 (17) |
| Corticosteroids*       | 13 (20) | 31 (17) |
| Antifibrinolytic (aminocaproic acid or tranexamic acid) | 6 (9) | 14 (8) |
| Azathioprine           | 1 (2) | 1 (0.6) |
| Red blood cell transfusion | 1 (2) | 1 (0.6) |
| Platelet transfusion   | 1 (2) | 2 (1) |

Pt-yr: patient-years.

*Corticosteroids include prednisone/prednisolone, methylprednisolone, and dexamethasone.
| Investigator                  | Institution                                                                 | Country      |
|------------------------------|-----------------------------------------------------------------------------|--------------|
| Abish, Sharon                | Montreal Children’s Hospital                                                | Canada       |
| Barnes, Chris                | The Royal Children’s Hospital                                               | Australia    |
| Beam, Donald                 | Cook Children’s Medical Center                                              | USA          |
| Bennett, Carolyn             | Emory University                                                            | USA          |
| Blanchette, Victor           | The Hospital for Sick Children                                              | Canada       |
| Bussel, James                | New York Presbyterian Hospital, Weill Cornell Medical Center               | USA          |
| Callaghan, Michael           | Children’s Hospital of Michigan                                            | USA          |
| Despotovic, Jenny            | Texas Children’s Hospital West Tower                                       | USA          |
| Diaz de Heredia Rubio, Cristina | Hospital Universitari Vall d Hebron                              | Spain        |
| Escoto, Heather              | Peyton Manning Children’s Hospital at St Vincent                            | USA          |
| Ford, James                  | Children’s Hospital and Medical Center                                      | USA          |
| Geddis, Amy                  | University of California at San Diego, Rady Children’s Hospital San Diego   | USA          |
| Guerrera, Michael            | Children’s National Medical Center                                         | USA          |
| Ho, Richard                  | Vanderbilt University Medical Center, Monroe Carell Junior Children’s Hospital at Vanderbilt | USA |
| Ikeda, Alan                  | Children’s Specialty Center of Nevada                                      | USA          |
| Kalpathi, Ramasubramanian    | Children’s Mercy Hospital                                                   | USA          |
| Nugent, Diane                | Children’s Hospital of Orange County                                       | USA          |
| Pastore, Yves                | Centre Hospitalier Universitaire Sainte-Justine                            | Canada       |
| Quinn, Charles               | Cincinnati Children’s Hospital Medical Center                               | USA          |
| Raj, Ashok                   | Pediatric Cancer and Blood Disorders Clinic                                 | USA          |
| Ritchey, Arthur              | Children’s Hospital of Pittsburgh of University of Pittsburgh Medical Center | USA          |
| Rose, Melissa                | Nationwide Children’s Hospital                                              | USA          |
| Russell, Susan               | Sydney Children’s Hospital                                                  | Australia    |
| Stegner, Martha              | University of Texas Southwestern Medical Center                             | USA          |
| Tarantino, Michael           | The Bleeding and Clotting Disorders Institute                               | USA          |
| Thompson, Alexis             | Ann and Robert H Lurie Children’s Hospital of Chicago                       | USA          |
| Velez, Maria                 | Children’s Hospital                                                         | USA          |
| Williams, Bronwyn/Roy, John  | Children’s Health Queensland                                                | Australia    |
Figure S1. Study guidelines for romiplostim dosage and discontinuation.

**Continuing romiplostim from parent study (last dose within 24 weeks)**
- Yes: Continue romiplostim at same dosage
- No: Start romiplostim at 1 μg/kg/week

**Dosage adjustments for platelet counts during the study**

| Platelet count                  | Romiplostim Dose                  |
|--------------------------------|----------------------------------|
| < 50x10^9/L                    | Increase by 1 μg/kg/week*         |
| 50 to 200x10^9/L               | Dosage remains constant*          |
| > 200 to < 400x10^9/L for 2 consecutive weeks | Reduce by 1 μg/kg/week*†‡        |
| ≥ 400x10^9/L                   | Withhold the dose; when platelets return to < 200x10^9/L, reduce by 1 μg/kg/week at next dose*†‡§ |

**Possible reasons to withhold romiplostim doses:**
1. Required - any platelet count is ≥ 400x10^9/L
2. Required - current dose is 1 μg/kg/week and a dose reduction is required
3. Investigator’s opinion - the patient maintains an acceptable platelet count ≥ 50x10^9/L without weekly romiplostim treatment

* Romiplostim may be used with other medical ITP therapies. If platelet count is ≥ 50x10^9/L, other medical ITP therapies may be reduced or discontinued.
† If platelet count is elevated in response to the initiation or increase in dose of another ITP medication, then the same dose of romiplostim should be administered when the platelet count is < 200x10^9/L.
‡ If the current dose is 1 μg/kg and a dose reduction is required during the treatment period, the dose will be withheld until the platelet count falls to < 50x10^9/L. Once the platelet count is < 50x10^9/L, dosing of romiplostim will resume at a dose of 1 μg/kg using the dose adjustment rules above.
§ If platelet count is ≥ 400x10^9/L due to rescue medications, it is at the discretion of the investigator to reduce the dose of romiplostim by 1 μg/kg.
Figure S2. Platelet counts and romiplostim dosing in patients with an SAE of low platelet count

Gr: grade; plt: platelets; SAE: serious adverse event.
Figure S3A. Rescue medication use over time

Figure S3B. Concomitant medication use over time

ITP: immune thrombocytopenia.
Figure S4. Platelet counts and romiplostim doses for each patient with a treatment-free response.
There were 3 months between the phase 3 and extension studies.

PBO: placebo.