# SUPPLEMENTARY MATERIAL

## Exhibit S1. Notes on HCRU Missing Data Imputation, Costing Methods, and General Assumptions

Costs were estimated for all HCRU, regardless of whether the AE was deemed to have been caused by the study drug, there was clarity regarding whether the resource was indeed used to treat the AE, and whether other AEs coincided with the AE of interest. The following additional general rules and assumptions were applied to perform the costing.

### Severity

When AE Severity was recorded as Severe, it was considered as grade 3; when AE Severity was recorded as Life-threatening/Severe, it was considered as grade 4.

### AE Event

When one patient had more than one AE, the AEs were differentiated based on start dates and end dates, given no overlap.

## Hospitalizations

Cost per Hospitalization: Hospitalization LOS \* Hospitalization Cost/Day

Hospitalization Cost/Day: Estimated using HCUP data on average cost and average LOS for hospitalizations with AE as primary diagnosis, using Medicare costs

Hospitalization LOS: Hospitalization Discharge Date – Hospitalization Admission Date + 1

---When hospitalization admission or discharge date was unavailable, assumed HCUP average LOS for that AE

---When hospitalization admission date preceded AE start date, replaced hospitalization admission date with AE start date

---When hospitalization discharge date was after AE end date, replaced hospitalization discharge date with AE end date +1 (to provide 1 day from confirming conclusion of AE to discharge)

## Ed Visits

ED Visit Cost Notes: The cost of an ED visit was included as a separate component in the calculation of the cost of the AE even though the ED visits typically coincided with a date of hospital admission. The source for the cost of an ED visit described it as the cost of an ED visit not resulting in admission, based on lack of data on the cost of the ED visit itself when a patient is admitted to the hospital. This may lead to an over- or underestimate of the cost of an ED visit.

## Medications and Medication Administration

Cost per Event of Medication: Units/Day \* Cost/Unit \* Days of Medication Use (e.g., #mg/day \* $/mg \* #days)

Cost per Event of Medication Administration: Cost/Administration \* Administrations/Day \* Days of Medication Use

Medication Cost Notes: Costs of medication wastage were not included. For example, costs for medications administered via IV injection were not rounded up to reflect use of whole vials. The exception is in the case of a patch, where the full cost of a patch was assumed regardless of whether the duration of use was less than the maximum recommended duration of use of the patch.

Medication and medication administration costs were included as a separate component in the calculation of the cost of the AE regardless of whether the duration of the medication overlapped with the duration of a hospitalization (during which the cost of medications would be expected to be incorporated into the cost of the hospitalization). The only exception was in the single instance, which was for nausea, where IV fluid hydration was listed as a resource used. The cost of IV fluid hydration was assumed to be included in the cost of hospitalization. The inclusion of medication costs as a separate component in the calculation of the cost of the AE may lead to an overestimate of the cost of the AE.

Medication Mapping: For drugs listed in the patient narratives that were marketed only outside the US or for which a price was not available in RedBook (e.g., because discontinued) or Walgreens.com in the case of OTC drugs, a similar drug in terms of mechanism of action or purpose was selected, based on guidance from the medical advisor.

Medication Formulation: Each event of use of a medication was costed assuming a particular form (e.g., tablet) for that medication. When the form of the medication was not available in the patient narrative, the form corresponding with the medication’s indication for the AE was assumed. For nausea, when the form of the medication was not available in the patient narrative, and costing data were available in RedBook for multiple forms, and the medication’s indication did not suggest a particular form for nausea and did not seem to restrict a particular form to a non-nausea use, an oral form was assumed. In addition, the form most compatible with nausea was selected, based on guidance from our medical advisor. For example, if a drug was available as an orally disintegrating tablet and as a (non–orally disintegrating) tablet, the orally disintegrating tablet was selected. Note that although patients experiencing severe nausea may not be able to tolerate IV medications, the assumptions were made that orals were used versus IV drugs because of many long durations of medication use, most of which occurred outside the window of a hospitalization. Based on a face validity check, assuming use of IV medications for long periods of time seemed impractical and yielded unreasonably high medication administration costs.

Medication Unit Cost: The medication cost per unit (e.g., mg) for each medication was calculated as the average of the costs for the form selected (e.g., tablet) from RedBook.

Medication Duration, IV Injections: When the estimated medication duration exceeded the maximum duration of use of a medication per its labeled indication, the medication duration was reset to the maximum duration. When the medication start date was unavailable, the AE start date was used instead. When the medication end date was unavailable, the medication end date was assumed equal to the medication start date (resulting in 1 days’ worth of IV injections for that medication). When both the medication start date and the AE start date were unavailable and/or the medication end date and the AE end date were unavailable and there was no mention of duration of use in the medication’s indication, the duration of medication use was assumed to be one day. Assumptions of 1 days’ worth of IV injections may over- or underestimate the cost of AEs treated with IV medications, depending on the alternative duration and cost of treatment with an oral version.

Medication Duration, all other medications: When the medication start date was unavailable, the AE start date was used instead. When the medication end date was unavailable, the AE end date was used instead. When both the medication start date and the AE start date were unavailable and/or the medication end date and the AE end date were unavailable, the duration of medication use was assumed based on the average duration of use of medications in instances where medication start and end dates were available with no assumptions required.

When the estimated medication duration exceeded the maximum duration of use of a medication per its labeled indication, the medication duration was reset to the maximum duration. In the case of a patch, each patch was assumed to be used up to the maximum duration indicated for the patch, or the end of the estimated medication duration, whichever was earlier. When the maximum duration indicated for the patch preceded the end of the estimated medication duration, the cost of another patch was incurred. This was repeated for the entire estimated medication duration. Patch costs were not prorated.

Table S1. Unit Costs for HCRU Other Than Medications

|  | Unit Cost (2017 US$) | Source |
| --- | --- | --- |
| Cost per day of hospitalization: nausea | $2,414.20 | Derived using mean cost inflated to 2017 USD (BLS, 2017) ($6,250.63) and mean LOS (2.589 days) per Medicare hospitalization. HCUP (2018). 2014 National Diagnoses--ICD-9-CM Codes (ICD9), Principal Diagnosis: 787.02 Nausea Alone (n=1010). |
| Cost per day of hospitalization: thrombocytopenia | $2,421.86 | Derived using mean cost ($11,244.33) and mean LOS (4.643 days) per Medicare hospitalization. HCUP (2017). 2014 National Diagnoses--ICD-9-CM Codes (ICD9), Principal Diagnosis: 287.49 Sec Thrombocytopenia NEC (n=1540). |
| ED visit | $1,326.74 | CDC (2012). |
| IV injection (for medication administration) | $69.98 | CMS (2017). CPT code 96365, Therapeutic, Prophylactic, and Diagnostic Injections and Infusions. |
| CT scan | $252.74 | CMS (2018a). CPT code 74160, CT Abdomen with dye.  |
| Wound care  | $168.95 | CMS (2018a). CPT code 97602, Wound(s) care nonselective.  |
| Platelet count | $5.53 | CMS (2018b). CPT code 85049, Automated platelet count. |
| Venipuncture (added to cost of Platelet Count) | $3.00 | CMS (2018b). CPT code 36415, Routine venipuncture.  |
| Platelet transfusion | $375.07 | CMS (2018a). CPT code 36430, Blood transfusion service. |
| Blood transfusion service (added to cost of platelet transfusion) | $35.53 | CMS (2017). CPT code 36430, Blood transfusion service |
| Platelets (added to cost of platelet transfusion) | $624.66 | CMS (2018b). CPT Code P9037, Platelets, pheresis, leukocyte-reduced, irradiated. |

BLS = Bureau of Labor Statistics; CDC = Centers for Disease Control and Prevention; CMS = Centers for Medicare and Medicaid Services; CPT = Current Procedural Terminology; CT = computed tomography; ED = emergency department; HCUP = Health Care Cost and Utilization Project; ICD-9-CM = International Classification of Diseases 9th Edition Clinical Modification; IV = intravenous; LOS = length of stay; NEC = not elsewhere classified.

Table S2. Extent of Missing Data for Prescription Duration: Nausea

|  | n (%) |
| --- | --- |
| Number of unique instances of medication use recorded in narratives | 77 |
| Number of instances for which both the start date and end date were provided | 44 (57.1%) |
| Number of instances for which only the start date was provided | 16 (20.8%) |
| Number of instances for which neither the start nor end date were provided | 17 (22.1%) |

Note: In all instances for which the medication end date was provided, the start date also was provided.

## Supplemental References

Bureau of Labor Statistics (BLS). Inflation & prices: medical care services in U.S. city average, all urban consumers, not seasonally adjusted. 2017. [cited 2017 October 12] Available from: <https://www.bls.gov/data/>.

Centers for Disease Control and Prevention (CDC). Health, United States, with special feature on emergency care (Data table for Figure 29), 2012. [cited 2017 December 27] Available from: http://www.cdc.gov/nchs/data/hus/hus12.pdf.

Centers for Medicare & Medicaid Services (CMS). Physician fee schedule. 2017. [cited 2017 December 27] Available from: <https://www.cms.gov/apps/physician-fee-schedule/overview.aspx>.

Centers for Medicare & Medicaid Services (CMS). Addendum B. January 2018a. [cited 2017 December 27] Available from: <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Addendum-A-and-Addendum-B-Updates.html?DLSort=2&DLEntries=10&DLPage=1&DLSortDir=descending>.

Centers for Medicare & Medicaid Services (CMS). Clinical Laboratory Fee Schedule. 2018b v1. [cited 2017 December 28] Available from: <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files.html>.

HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. [cited 2018 February 20] Available from: <https://hcupnet.ahrq.gov/>.