# Supplementary appendix - Tables

**Table A: Inclusion and exclusion criteria for the clinical systematic literature review**

| **Category** | **Inclusion criteria** | **Exclusion criteria** |
| --- | --- | --- |
| Population | Adult patients with AdvSM, which includesa:  ASM  SM-AHN  MCL | Patients with cutaneous mastocytosis, indolent or smoldering SM  Patients with disease other than AdvSM  Pediatric population  Healthy volunteers |
| Interventions | All pharmacological interventions such as but not limited to avapritinib, midostaurin, cladribine and imatinib | Any non-pharmacological Interventions |
| Comparators | Placebo  SC (authors defined)  Any other pharmacological/non-pharmacological intervention (such as HSCT)  No comparator limit for single-arm trials | No limit on comparators |
| Outcomes (tentative list, not exhaustive) | Overall response rate (including complete and partial remission and their definitions)  Survival (including overall survival, progression-free survival and event-free survival)  Duration of response  Treatment effect on HRQL (including patient-reported outcomes)  Mastocytosis Symptom Assessment Form score  Incidence of adverse events  Study/treatment discontinuation (including proportion of patients and time to discontinuation)  Pure pathologic response  Subgroup extracted:  Disease sub-types of AdvSM  Line of therapy | Studies assessing outcomes not relevant to the review |
| Study design | RCTs  Non-RCTs  Single-arm trials  Retrospective and prospective cohort studies  Real-world evidence studies  Systematic review and meta-analysis of RCTs/observational studiesb | Reviews, letters, comments and editorials  Case studies or case reports  Economic studies |
| Language | English only | Non-English publications |
| Countries | No restrictions | None |
| **Key:** AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; HRQL, health-related quality of life; HSCT, hematopoietic stem-cell transplantation; MCL, mast cell leukemia; RCT, randomized controlled trial; SLR, systematic literature review; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; SC, standard care.  **Note:** a Studies assessing mixed population of SM were included at the abstract/title screening stage. At the full text screening stage, studies were only included if data were reported separately for AdvSM or its subgroups: MCL, ASM, SM-AHN. Furthermore, for all the studies included during the secondary screening stage, the definitions and criteria used for the disease were captured in the data extraction grid.  b Bibliographies of systematic review and meta-analysis articles were screened to ensure that all relevant studies were identified in the SLR. | | |

**Table B: Summary of inclusion/exclusion of studies for ITCs**

| **Study name** | **Trial name** | **Treatment/comparator** | **Relevance of study** |
| --- | --- | --- | --- |
| **Single-arm trials** | | | |
| Gotlib 2020 | EXPLORER | Avapritinib | Included |
| Blueprint (BLU-285-2202) | PATHFINDER | Avapritinib | Included |
| Gotlib 2016 | D2201 | Midostaurin | Included |
| DeAngelo 2018 | A2213 | Midostaurin | Included |
| Papayannidis 2014 | NR | Midostaurin | Excluded – sample size ≤ 10 |
| Vega-Ruiz 2009 | NR | Imatinib mesylate | Excluded – not a treatment of interest |
| Kluin-Nelemans 2003 | NR | Cladribine | Excluded – not a treatment of interest |
| Parikh 2010 | NR | Everolimus | Excluded – not a treatment of interest |
| Lübke 2019 | NR | Avapritinib + midostaurin | Excluded – not a treatment of interest |
| Gotlib 2019 | NR | Brentuximab vedotin | Excluded – not a treatment of interest |
| Verstovsek 2008 | NR | Dasatinib | Excluded – not a treatment of interest |
| Jawhar 2017a | NR | * Salvage therapy * Intensive chemotherapy / hypomethylating agents * Intensive chemotherapy followed by allogeneic stem-cell transplantation | Excluded – not treatments of interest |
| Dybedal 2016 | NR | Midostaurin | Excluded – sample size ≤ 10 |
| Gotlib 2010 | NR | Midostaurin | Excluded – no comparable endpoints reported |
| Jawhar 2017b | NR | Midostaurin | Excluded - pooled analysis of D2201 and compassionate use program |
| Gruson 2013 | NR | Thalidomide | Excluded – not a treatment of interest |
| Hochhaus 2015 | NR | Nilotinib | Excluded – not a treatment of interest |
| Pardanani 2003 | NR | Imatinib mesylate | Excluded – not a treatment of interest |
| Hermine 2010 | NR | Cladribine | Excluded – not a treatment of interest |
| Casassus 2002 | NR | Interferon-alpha | Excluded – not a treatment of interest |
| **Observational studies** | | | |
| Chandesris 2016 | NR | * Midostaurin * Historical control | Excluded - A2213, D2201, and French compassionate use of midostaurin program and a historical control of patients who did not receive midostaurin (CEREMAST) |
| Chandesris 2014 | NR | * Midostaurin * Historical control | Excluded - French compassionate use of midostaurin program and a historical control of patients who did not receive midostaurin (CEREMAST) |
| Rastogi 2013 | NR | * Tyrosine-kinase inhibitor * Azacitidine/ cytarabine/ Allogeneic hematopoietic stem-cell transplantation * Azacitidine * JAK2 inhibitor * Lenalidomide * Tyrosine-kinase inhibitor + azacitidine * Eltrombopag, hydrea * Prednisone, symptomatic | Excluded – not treatments of interest |
| Reiter 2017 | NR | * Midostaurin * Historical control | Excluded - Pooled analysis of D2201 and A2213 patients whose date of diagnosis was known compared with a German historical control |
| Pardanani 2009 | NR | * Interferon-alpha (± prednisone) * Hydroxyurea * Imatinib mesylate * Cladribine | Excluded – not treatments of interest |
| Jain 2017 | NR | * Imitanib * Dasatinib * Cladribine * Allogeneic stem-cell transplant | Excluded – not treatments of interest |
| Pagano 2008 | NR | * Imatinib * Conventional chemotherapy * Interferon-alpha * Cladribine * Allogeneic hematopoietic stem-cell transplantation * Steroids | Excluded – not treatments of interest |
| Lim 2009 | NR | * Hydroxyurea * Imatinib mesylate * Interferon-alpha with or without prednisone * Cladribine | Excluded – not treatments of interest |
| Jawhar 2017c | NR | * Midostaurin * Cladribine * Midostaurin and cladribine | Excluded - Case series of MCL patients from pooled analysis of D2201 and compassionate use program |
| Helbig 2020 | NR | Cladribine | Excluded – not treatments of interest |
| Barete 2015 | NR | Cladribine | Excluded – not treatments of interest |
| **Key:** JAK, Janus kinase; MCL, mast cell leukemia; NR, not reported. | | | |

|  |  |  |
| --- | --- | --- |
| **EXPLORER and PATHFINDER**  **(WHO criteria)** | **D2201**  **(Gotlib 2016, Table S6)** | **A2213**  **(DeAngelo 2018, Supp. Table 2A)** |
| Total number: 5 | Total number: 8 | Total number: 10 |
| ANC < 1.0 x 109 /L or hemoglobin < 10 g/dL or platelets < 100 x 109 /L | Anemia (hemoglobin < 10 g/dL) | Anemia (hemoglobin < 10 g/dL) |
| Thrombocytopenia (platelets < 100×109/L) | Thrombocytopenia (platelets < 100×109/L) |
| Neutropenia (absolute neutrophil count < 1×109/L) | Neutropenia (absolute neutrophil count < 1×109/L) |
| Hepatomegaly with impaired liver function - i.e., elevated transaminases and/or bilirubin levels and/or hypoalbuminemia (with or without ascites or portal hypertension) | Increased total bilirubin | Increased total bilirubin |
| Increased ALT | Increased ALT |
| Increased AST | Increased AST |
|  |  | Ascites |
| Malabsorption with hypoalbuminemia and/or significant weight loss defined as > 10% weight loss over the last 6 months | Hypoalbuminemia | Hypoalbuminemia |
| Weight loss (medically documented loss of ≥ 10% of body weight within 6 months prior to study) | Weight loss (medically documented loss of at least 10% of body weight within 12 months prior to study) |
| Palpable splenomegaly with hypersplenism (e.g., as documented by thrombocytopenia i.e., platelets < 100 x 109 /L) |  |  |
| Skeletal involvement with large osteolytic lesions and/or pathologic fractures |  | Lytic bone lesions |
| Key: ALT, alanine transaminase; ANC, absolute neutrophil count; AST, **aspartate aminotransferase.** | | |

**Table C: Comparison of C-findings at baseline**

**Table D: Baseline characteristics across studies – safety population and FAS**

| **Study** | **EXPLORER** | **PATHFINDER** | **A2213** | **D2201** |
| --- | --- | --- | --- | --- |
| **Treatment** | Avapritinib | Avapritinib | Midostaurin | Midostaurin |
| **Population** | Safety  (N = 69) | Safety  (N = 62) | FAS  (N = 26) | FAS  (N = 116) |
| **Age (years), median (range)** | 67 (34, 83) | 68.5 (31, 88) | 64.5 (24, 79) | 63.0 (25, 82) |
| **Sex, n (%)** | | | | |
| **Male** | 41 (59) | 34 (55) | 15 (58) | 76 (66) |
| **Female** | 28 (41) | 28 (45) | 11 (42) | 40 (34) |
| **Race, n (%)** | | | | |
| **White** | 61 (88) | 54 (87) | 21 (81)c | 111 (96) |
| **Other** | 3 (4)e | 7 (11) | NR | 3 (3) |
| **Unknown** | 5 (7) | 1 (2) | NR | 2 (2) |
| **ECOG performance status, n (%)** | | | | |
| **0/1** | 48 (70) | 43 (69) | 12 (46) | 77 (66) |
| **2/3** | 21 (30) | 19 (31) | 14 (54) | 39 (34) |
| **Prior therapy, n (%)** | | | | |
| **No** | 28 (41) | 20 (32) | 5 (19) | 64 (55) |
| **Yes** | 41 (59) | 42 (68) | 21 (81) | 52 (45) |
| **Subtype of AdvSM, n (%)** | | | | |
| **ASM** | 8 (12) | 9 (15) | 3 (12) | 22 (19) |
| **SM-ANH** | 48 (70) | 43 (69) | 17 (65) | 73 (63) |
| **MCL** | 13 (19) | 10 (16) | 6 (23) | 21 (18) |
| ***KIT* D816V mutation status, n (%)** | | | | |
| **Positive** | 64 (93) | 59 (95) | 19 (77) | 94 (81.0) |
| **Negative** | 5 (7) | 3 (5) | 5 (19) | 13 (11.2) |
| **Other/Unknown** | 0 (0) | 0 (0) | 1 (4)a | 9 (7.8)b |
| **Bone marrow mast cell burden (%), median (range)** | 40 (5, 95) | 45 (1, 95) | 50 (5, 95) | 40 (3, 98) |
| **Serum tryptase level (μg/L), median (range)** | 173.3  (12.4, 1414.3) | 282.6  (23.8, 1600.0) | 323  (22, 1255) | 200  (2, 12069) |
| **Number of C-findings per patient, n (%)** | | | | |
| **0** | 7 (10) | 18 (29) | 0 | NR |
| **1** | 31 (45) | 24 (39) | 3 (12) | 31 (27) |
| **2** | 16 (23) | 12 (19) | 10 (38) | 20 (17) |
| **≥ 3** | 15 (22) | 8 (13) | 13 (50) | 38 (33) |
| **Key:** AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; MCL, mast cell leukemia; NR, not reported; PEP, primary efficacy population; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with associated hematological neoplasm.  **Note: a** – The patient was positive for the *KIT* S451C mutation.  b– For 5 patients the *KIT* D816V mutation status was unknown, 3 were positive for the *KIT* D816Y mutation and 1 had a different mutation.  C– This number was calculated by subtracting the proportion of Caucasians in D2201 from the pooled analysis of  D2201 and A2213 presented in the Australian Public Assessment Report. | | | | |

**Table E: Overall survival results**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Avapritinib population** | **Midostaurin population** | **Matching variables** | **ESS** | **Naïve ITC,**  **HR (95% CI)** | **MAIC,**  **HR (95% CI)** |
| Pooled PATHFINDER and EXPLORER (RAC-RE), N = 85 | Pooled D2201 and A2213 PEP,  N = 115 | Age, AdvSM subtype, race | 68.1 | 0.54 (0.32, 0.92) | 0.44 (0.25, 0.76) |
| Pooled PATHFINDER and EXPLORER (Safety), N = 131 | Pooled D2201 and A2213 FAS, N = 142 | Age, AdvSM subtype, race | 108.8 | 0.52 (0.32, 0.85) | 0.42 (0.25, 0.71) |
| PATHFINDER (RAC-RE), N = 32 | Pooled D2201 and A2213 PEP, N = 115 | Age, AdvSM subtype | 25.2 | 0.51 (0.18, 1.45) | 0.51 (0.17, 1.57) |
| Pooled PATHFINDER and EXPLORER (RAC-RE, prior therapya), N = 55 | Pooled D2201 and A2213 PEP,  N = 115 | Age, AdvSM subtype, Race | 39.3 | 0.50 (0.26, 0.96) | 0.39 (0.19, 0.80) |
| Pooled PATHFINDER and EXPLORER (RAC-RE, mido-naïveb), N = 51 | Pooled D2201 and A2213 PEP,  N = 115 | Age, AdvSM subtype, race | 44.9 | 0.43 (0.22, 0.84) | 0.37 (0.19, 0.73) |
| Pooled PATHFINDER and EXPLORER (RAC-RE, 200 mgc), N = 44 | Pooled D2201 and A2213 PEP,  N = 115 | Age, AdvSM subtype | 32.8 | 0.67 (0.31, 1.42) | 0.59 (0.27, 1.32) |
| **Key:** ASM, aggressive systemic mastocytosis; CI, confidence interval; ESS, effective sample size; FAS, full analysis set; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; MCL, mast cell leukemia; Mido, midostaurin; OS, overall survival; PEP, primary efficacy population; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with associated hematological neoplasm.  **Notes:** a – Patients who had prior systemic therapy.  b - Patients with no prior midostaurin treatment.  c - Patients who received a 200 mg starting dose. | | | | | |

**Table F: Overall response rate results**

| **Avapritinib population** | **Avapritinib ORR (%)** | **Midostaurin population** | **Midostaurin**  **ORR (%)** | **Matching variables** | **ESS** | **Naïve ITC,**  **OR (95% CI)** | **MAIC,**  **OR (95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Pooled PATHFINDER and EXPLORER (RAC-RE), N = 79 | 69.62% | D2201 PEP,  N = 89 | 35.96% | Age, AdvSM subtype, race, ECOG PS, *KIT* D816V mutation status, bone marrow mast cell burden | 53.9 | 4.08 (2.14, 7.79) | 4.06 (3.09, 5.33) |
| PATHFINDER (RAC-RE), N = 31 | 64.52% | D2201 PEP,  N = 89 | 35.96% | Age, AdvSM subtype, race, ECOG PS, *KIT* D816V mutation status, bone marrow mast cell burden | 23.3 | 3.24 (1.38, 7.61) | 3.78 (2.31, 6.19) |
| Pooled PATHFINDER and EXPLORER (RAC-RE, prior therapya), N = 53 | 66.04% | D2201 PEP,  N = 89 | 35.95% | Age, AdvSM subtype, race, ECOG PS, *KIT* D816V mutation status, bone marrow mast cell burden | 40.0 | 3.46 (1.70, 7.08) | 4.04 (2.96, 5.52) |
| Pooled PATHFINDER and EXPLORER (RAC-RE, mido-naïveb), N = 46 | 76.09% | D2201 PEP,  N = 89 | 35.96% | Age, AdvSM subtype, race, ECOG PS, *KIT* D816V mutation status, bone marrow mast cell burden | 30.5 | 5.67 (2.54, 12.66) | 3.83 (2.25, 6.53) |
| Pooled PATHFINDER and EXPLORER (RAC-RE, 200 mgc), N = 42 | 57.14% | D2201 PEP,  N = 89 | 35.96% | Age, AdvSM subtype, race, ECOG PS, *KIT* D816V mutation status, bone marrow mast cell burden | 28.8 | 2.37 (1.12, 5.02) | 2.85 (1.96, 4.15) |
| **Key:** ASM, aggressive systemic mastocytosis; ava, avapritinib; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; MCL, mast cell leukemia; Mido, midostaurin; OR, odds ratio; ORR, overall response rate; PEP, primary efficacy population; RAC-RE, response assessment committee response-evaluable; SM-AHN, systemic mastocytosis with associated hematological neoplasm.  **Notes:** a – Patients who had prior systemic therapy.  b - Patients with no prior midostaurin treatment.  c - Patients who received a 200 mg starting dose. | | | | | | | |

**Table G: Complete remission results**

| **Avapritinib population** | **Avapritinib CR (%)** | **Midostaurin population** | **Midostaurin CR (%)** | **Matching variables** | **ESS** | **Naïve ITC, OR (95% CI)** | **MAIC, OR (95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Pooled PATHFINDER and EXPLORER (RAC-RE), N = 79 | 12.66% | D2201 PEP,  N = 89 | 1.12% | Age, AdvSM subtype, Race, ECOG PS, *KIT* D816V mutation status, bone marrow mast cell burden | 53.9 | 12.75  (1.59, 102.05) | 9.56  (0.97, 93.81) |
| Pooled PATHFINDER and EXPLORER (RAC-RE, prior therapya), N = 53 | 13.21% | D2201 PEP,  N = 89 | 1.12% | Age, AdvSM subtype, Race, ECOG PS, *KIT* D816V mutation status, bone marrow mast cell burden | 40.0 | 13.39  (1.60, 112.17) | 10.44  (0.96, 113.57) |
| Pooled PATHFINDER and EXPLORER (RAC-RE, mido-naïveb), N = 46 | 17.39% | D2201 PEP,  N = 89 | 1.12% | Age, AdvSM subtype, Race, ECOG PS, *KIT* D816V mutation status, bone marrow mast cell burden | 30.5 | 18.53  (2.24, 153.33) | 12.39  (1.14, 134.58) |
| **Key:** AdvSM, advanced systemic mastocytosis; CI, confidence interval; CR, complete remission; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample sizes; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; Mido, midostaurin; OR, odds ratio; PEP, primary efficacy population; RAC-RE, response assessment committee response-evaluable.  **Notes:** a – Patients who had prior systemic therapy.  b - Patients with no prior midostaurin treatment. | | | | | | | |

**Table H: Summary of overall response rates and complete remission rates by the IWG-MRT-ECNM response criteria**

|  |  |  |
| --- | --- | --- |
| **Population** | **ORR (%)** | **CR (%)** |
| Pooled PATHFINDER and EXPLORER RAC-RE, N = 79 | 69.62% | 12.66% |
| EXPLORER (RAC-RE), N = 48 | 72.92% | 20.83% |
| PATHFINDER (RAC-RE), N = 31 | 64.52% | 0.00% |
| D2201 PEP, N = 89 | 35.96% | 1.12% |
| **Key:** CR, complete remission; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis; ORR, overall response rate; PEP, primary efficacy population; RAC-RE, response assessment committee response-evaluable. | | |