

## SUPPLEMENTAL MATERIAL

### HEMODIAFILTRATION TO ADDRESS UNMET MEDICAL NEEDS IN END-STAGE KIDNEY DISEASE PATIENTS

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**Appendix 1:** Members of the Kidney Health Initiative “Regulatory Policies and Positions Affecting Device Approval in the US: Tools to Assess the Process and Foster Device Development for Patients with Kidney Disease” Workgroup’s Hemodiafiltration Subgroup and their affiliations

**Supplemental Table 1:** Observational cohort studies comparing mortality with HDF and hemodialysis

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**Supplemental Table 1:** Observational cohort studies comparing mortality with HDF and hemodialysis

| Study         | Study Design                        | Treatment Modalities <sup>1</sup> | Dilution Mode <sup>2</sup> | Number of Patients | Convection Volume (L/session) <sup>3</sup> | Type of Analysis <sup>4</sup> | Hazards Ratio for All-cause Mortality <sup>5</sup> |
|---------------|-------------------------------------|-----------------------------------|----------------------------|--------------------|--|-------------------------------|--|
| Locatelli [1] | Retrospective                       | lfHD + hfHD (Ref)                 |                            | 6298               | -  | Adj Cox model                 | 0.90 [0.77 – 1.06]                                 |
|               |                                     | Hemofiltration + HDF              | NR                         | 1082               | NR   |                               |  |
| Canaud [2]    | Prospective<br>Prevalent patients   | lfHD + hfHD (Ref)                 |                            | 1912               |  | Adj Cox model                 | 0.92 (p = 0.066)                                   |
|               |                                     | HDF (Low volume)                  | Post                       | 156                | 5 – 14.9                                   |                               |  |
|               |                                     | HDF (High volume)                 | Post                       | 97                 | 15 - 25                                    |                               |  |
| Panichi [3]   | Prospective<br>Prevalent patients   | lfHD + hfHD (Ref)                 |                            | 424                |  | Adj Cox model                 | 0.78 (p < 0.01)                                    |
|               |                                     | HDF (low volume)                  | Post                       | 204                | 10 – 15                                    |                               |  |
|               |                                     | HDF (high volume)                 | Post                       | 129                | 22 – 25                                    |                               |  |
| Vilar [4]     | Retrospective<br>Incident patients  | hfHD (Ref)                        |                            | 626                |  | Adj Cox model                 | 0.45 [0.35 – 0.59]                                 |
|               |                                     | HDF                               | NR                         | 232                | NR   |                               |  |
| Imamović [5]  | Retrospective<br>Incident patients  | hfHD (Ref)                        |                            | 151                |  | Adj Cox model                 | 0.84 [0.46 – 1.53]                                 |
|               |                                     | HDF (low volume)                  | Post                       | 133                | 17.7 [15.3-19.2] <sup>6</sup>              |                               |  |
|               |                                     | HDF (high volume)                 | Post                       | 158                | 23.3 [21.9-25.3] <sup>6</sup>              |                               |  |
| Siriopol [6]  | Retrospective<br>Prevalent patients | hfHD (Ref)                        |                            | 431                |  | PSM + Adj Cox model           | 0.62 [0.42 – 0.93]                                 |
|               |                                     | HDF                               | Post                       | 224                | 22.2 [18.1-34.1] <sup>6</sup>              |                               |  |
| Canaud [7]    | Retrospective<br>Incident patients  | hfHD (Ref)                        |                            | 795                |  | PSM + Adj Cox model           | 0.88 [0.67 – 1.15]                                 |
|               |                                     | HDF                               | Post                       | 795                | >21  |                               |  |

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|                   |                    |            |         |       |                               |           |                    |
|-------------------|--------------------|------------|---------|-------|-------------------------------|-----------|--------------------|
| Mercadal [8]      | Retrospective      | HD (Ref)   |         | 22881 |                               | Adj Cox   |                    |
|                   | Prevalent patients | HDF        | Post    | 2254  | NR                            | model     | 0.77 [0.67 – 0.87] |
| Maduell [9]       | Retrospective      | hfHD (Ref) |         | 506   |                               | PSM + Adj |                    |
|                   | Incident patients  | HDF        | Post    | 506   | 26.9 [24.6-28.8] <sup>6</sup> | Cox model | 0.76 [0.62 – 0.94] |
| Locatelli<br>[10] | Retrospective      | HD (Ref)   |         | 6555  |                               | Adj Cox   |                    |
|                   | Prevalent patients | HDF        | Mixture | 538   | 15.1 – 20                     | model     | 1.16 [0.97 – 1.40] |
|                   |                    | HDF        | Mixture | 1010  | > 20                          |           | 1.08 [0.92 – 1.28] |

1. lfHD = low-flux hemodialysis, hfHD = high-flux hemodialysis, HDF = hemodiafiltration, Ref = reference modality for Hazards Ratio.
2. Post = post-dilution, Mixture = combination of pre- post- and mid-dilution, NR = not reported
3. NR = Not reported
4. Adj Cox model = Cox proportional hazards regression model adjusted for covariates, PSM = Propensity score matching.
5. HR [95% confidence interval] or (significance of difference from reference modality).
6. Interquartile range

## REFERENCES FOR SUPPLEMENTAL TABLE 1

- 1 Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D. Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. *Kidney Int* 1999; 55:286-293.
- 2 Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, Klassen P, Port FK. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney Int* 2006; 69:2087-2093.
- 3 Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, Rindi P, Donati G, Antonelli A, Panicucci E, Tripepi G, Tetta C, Palla R. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. *Nephrol Dial Transplant* 2008; 23:2337-2343.
- 4 Vilar E, Fry AC, Wellsted Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. *Clin J Am Soc Nephrol* 2009; 4:1944-1953.
- 5 Imamović G, Hrvačević R, Kapun S, Marcelli D, Bayh I, Grassmann A, Scatizzi L, Maslovarić J, Canaud B. Survival of incident patients on high-volume hemodiafiltration compared to low-volume hemodiafiltration and high-flux hemodialysis. *Int Urol Nephrol* 2014; 46:1191-1200.
- 6 Siroopol D, Canaud B, Stuard S, Mircescu G, Nistor I, Covic A. New insights into the effect of haemodiafiltration on mortality: the Romanian experience. *Nephrol Dial Transplant* 2015; 30:294-301.
- 7 Canaud B, Bayh I, Marcelli D, Ponce P, Merello JI, Gurevich K, Ladanyi E, Ok E, Imamović G, Grassmann A, Scatizzi L, Gatti E. Improved survival of incident patients with high-volume haemodiafiltration: a propensity-matched cohort study with inverse probability of censoring weighting. *Nephron* 2015; 129:179-188.
- 8 Mercadal L, Franck JE, Metzger M, Torres PU, de Cornelissen F, Edet S, Béchade C, Vigneau C, Drüeke T, Jacquelinet C, Stengel B. Hemodiafiltration versus hemodialysis and survival in patients with ESRD: the French Renal Epidemiology and Information Network (REIN) registry. *Am J Kidney Dis* 2016; 68:247-255.

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- 9 Maduell F, Varas J, Ramos R, Martin-Melo A, Pérez-García R, Berdud I, Moresco F, Canaud B, Stuard S, Gaulty A, Aljama P, Merello JI. Hemodiafiltration reduces all-cause and cardiovascular mortality in incident hemodialysis patients: a propensity matched cohort study. *Am J Nephrol* 2017; 46:288-297.
- 10 Locatelli F, Karaboyas A, Pisoni RL, Robinson BM, Fort J, Vanholder R, Rayner HC, Kleophas W, Jacobson SH, Combe C, Port FK, Tentori F. Mortality risk in patients on hemodiafiltration versus hemodialysis: a 'real-world' comparison from the DOPPS. *Nephrol Dial Transplant* 2017; doi:10.1093/ndt/gfx277 [EPub ahead of print].