Online Supplement

DSMB organization

Per the Charter the TOPCAT DSMB was charged by the sponsor, the National Institutes of Heart, Lung and Blood (NHLBI), with "safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and monitoring the overall conduct of the study." In addition, the DSMB was asked to make recommendations to the NHLBI regarding, among other things, "efficacy of the study intervention; selection, recruitment, and retention of participants; adherence to protocol requirements; completeness, quality, and analysis of measurements; and notification of and referral for abnormal findings." The DSMB consisted of 6 voting members including the Chair, and a nonvoting Executive Secretary and nonvoting biostatistician from the NHLBI. The NHLBI Program Office with additional nonvoting liaison personnel provided relevant management expertise and logistical guidance. During the TOPCAT Trial the DSMB held regularly scheduled meetings approximately every 6 months, as well as unscheduled meetings as necessary. These reviews consisted of 1) an Open Session, attended by personnel from the NHLBI, the Clinical Trial Coordinating Center (CTCC, New England Research Institutes (NERI)), leadership of the Trial's Executive Committee (EC) that typically included the Steering Committee Chair and the Trial's Co-PIs, and the DSMB; 2) a Closed Session, attended by NHLBI designated staff, the CTCC and the DSMB, where confidential outcome and safety data were presented; and 3) an Executive Session, attended only by voting members of the DSMB and the Executive Secretary. In addition to the scheduled and unscheduled meetings, the DSMB Chair monitored selective safety data by masked treated arm on a monthly basis.

Enrollment

Pre-trial plans and projections, Recruitment dynamics

Pre-trial plans, enrollment projections and the DSMB response to the enrollment strategy are described in the main paper, where meetings and data reviews are listed in Figure 1.

Geographic discrepancies in recruitment and clinical course of patient populations

Emergence and detection; tactical responses

At the January 2008 scheduled review (Figure 1) Georgia had reached 115% of its pre-trial projected enrollment for this stage of the trial, Russia was at 58%, the U.S. 73%, Argentina 11%, Brazil had not begun enrolling and the percentage of patients from Russia + Georgia was 68% (Figure 3). It was noted that the prevalence of a history of myocardial infarction/angina was higher in Russian patients (39%/79% vs. 24%/34% in the U.S., 31%/50% in Canada, 13%/13% in Argentina and 17%/61% in Georgia), while the prevalence of orthopnea was considerably higher in the U.S. (25%), Canada (43%) or Argentina (38%) as compared with Russia (12%) or Georgia (6%). At the January 2008 DSMB review no country-specific event rate or serious adverse event (SAE) data were available. The average trial follow-up for randomized patients was 5.5 months, and only 23 patients had a primary event reported, with most unadjudicated. The DSMB was informed that the CTCC had supplied Russian, Georgian and South American sites with newly validated BNP assay kits for enrollment using the BNP criterion, and the trial was setting up a BNP Pilot program in Russia and Georgia, in order to allow comparison of the patients randomized through the hospitalization or biomarker pathways. NHLBI Program staff working with the trial leadership reported that part of the rationale for the BNP Pilot program in Russia and Georgia was a perception that cardiovascular SAEs were being reported less frequently from Russia/Georgia, with the possible implications including a lower primary endpoint event rate.

In August, 2008 the "first European war of the 21st century" (S1) broke out between the two Eastern European countries participating in TOPCAT, making it the first multinational clinical trial to have key enrollment countries engage in mutual military hostilities. Fortunately the TOPCAT study sites

in Russia and Georgia were outside the war zone, and at the September 2008 DSMB review trial activities in Georgia were reported as not having been affected by the two months of military hostilities.

Initial evidence that event rates were lower in Georgia or Russia was presented during the Closed Session of the September 2008 DSMB review (Figure 1) where data for 1,461 patients were available, representing ~55% of the original time projected total enrollment for the interval. Enrollment in Russia and Georgia was beginning to decrease as a percent of the total (Figure 3), but was still the majority at 60.5% vs. 36.4% in North America. Enrollment in Georgia was at 76% of its allotted final projection based on the original estimated sample size of 4,500, and was at 98% of the interval allotment based on the lowering of trial size that occurred at this meeting. Country-specific aggregate event rate data available for the first time revealed that Georgia's was low (2.0% compared to 5.4% overall and 9.0% in the U.S.). However, there were only 6 events in Georgia, 27 in Russia and 38 in the U.S. The DSMB recommended that the Trial leadership "encourage Georgian investigators to enroll sicker patients into the trial", which was subsequently amended to read "encourage Georgian Investigators to enroll patients as expected per the study protocol".

At the next DSMB review in April 2009 (Figure 1) the previously noted country-specific unadjudicated aggregate primary event rate patterns persisted, and are given in Table 1 and discussed in the text of the main paper. In addition, The DSMB reviewed adverse event rates by country, and found them to be appropriately reported with no concerns regarding the safety report. Data quality based on extensive site monitoring by the CTCC was assessed to be good overall with very few missed visits. Enrollment compliance data indicated that 99% of randomized patients met blood pressure and heart failure entry criteria.

In the March, 2010 review the DSMB undertook the first scheduled unblinded interim analysis, at approximately 33% of the expected primary events in 2,199 enrolled patients as of the data freeze from December 2009. Brazil was now active, and overall enrollment was at 63% of the new 3,515 total

enrollment target. The conditional power exceeded the 10% futility boundary, and country-specific hazard ratios were not reviewed.

In early October 2010 NHLBI Program Divisional leadership managing the trial held an unscheduled meeting with the DSMB Chair (Figure 1) to review results of the requested BNP Pilot project in Russia, and to discuss a review of source document hospitalization records (22 index heart failure hospitalization discharge summaries) that had been reviewed by an NHLBI Program staff member fluent in Russian. It was noted that the hospitalization records suggested that "very few patients" (only 2 or possibly 3 out of 22 total records reviewed) "had presentations consistent with heart failure." This was consistent with findings noted in previous DSMB report data suggesting higher rates of MI. The DSMB Chair reviewed the same (Russian translated) material and concluded "the presenting complaints, admission and discharge diagnoses indicated that the majority of patients were likely suffering from acute ischemic symptoms, not HF per se. Specifically, in the majority of patients there is no documentation that heart failure was a major component of the index hospitalization."

The BNP and NT-proBNP data from Russia were compared to data from other countries, which consisted of samples from subjects who had entered the trial via the prior heart failure hospitalization criterion, as well as data from patients who entered the trial based on the BNP/NT-proBNP criterion (Table S1). In the Americas, NP tests among subjects enrolled via HF hospitalization were done at the time of the hospitalization, while in Russia and Georgia NP tests were done on every enrolled patient where the test was available. The summary of the DSMB Chair review of these data included 1) the majority of patients from Russia (54%) and Georgia (64%) who were randomized based on a previous HF hospitalization had NPs that were within the normal range; and 2) only a small minority (9%) of US and Canadian patients enrolled based on HF hospitalizations had normal NP values. These concerns were expressed in written communication prior to an unscheduled October 2010 meeting with the NHLBI and CTCC, where the DSMB Chair outlined a "global" strategy recommending that the Steering Committee address the issue of apparently below HF threshold NP levels, and institute closer

monitoring of enrollment criteria for patients in both Russia and Georgia. The specific recommendation was that the qualifying HF hospitalization record (using a Case Report Form) include documentation of physical evidence of fluid overload, as well as HF symptoms in addition to dyspnea. In addition, the CTCC and NHLBI Program staff should continue to closely monitor enrolled patients in these regions, and the comment that "if these trends are not reversed discontinuation of enrollment would be the likely recommendation." The above stipulated strategy and recommendations were reviewed and accepted by the full DSMB at a scheduled meeting later in October, 2010 (Figure 1).

At that meeting the DSMB reviewed data from 2,732 patients for up to date country specific enrollment, and 2,642 patients (75% of target) for the second interim analysis based on the data freeze a month earlier planned for approximately 50% of the expected events. The conditional power estimate of 90% far exceeded the 15% efficacy futility boundary, and trial continuation was recommended. No country-specific hazard ratios were available for review, and this information was requested for the next planned interim analysis. At the October meeting the Steering Committee leadership commented that ischemic heart disease presentations had been previously observed in Russian patients in other heart failure trials. The Trial leadership and the CTCC pointed out that the apparent regional differences in NP values using the BNP Pilot data were subject to selection bias in the HF clinical event-obtained BNP/NT-proBNP values in the Americas. The DSMB recommended considering the feasibility of modifying the enrollment form to include a detailed list of the heart failure signs and symptoms during the index hospitalization. The Trial leadership indicated this was already collected in patients post randomization. The DSMB pointed out that this information needs to be available to qualify for enrollment. The Trial leadership considered the request and provided a counter-argument response in January 2011, noting that the collection of signs and symptoms from the record of the index hospitalization would require a protocol amendment, which would result in an increase in site burden and expenditure of resources. Additionally, the leadership pointed out that the impact of such action in Russia would only be on the estimated 50-60 patients remaining to be enrolled. An alternative strategy,

agreed to by the DSMB in an unscheduled meeting with the Trial leadership in March 2011, proposed use of accelerated site monitoring to verify HF diagnoses in Stratum I (history of HF hospitalization) subjects, in both Russia and Georgia. In discussing stopping or limiting enrollment in some countries, the Trial leadership again pointed out that such action may have a negative impact on the trial, not only in terms of recruitment but also on how the trial's results would be interpreted, a reality that was acknowledged by NHLBI Program Staff and the DSMB.

The data presented at the June, 2011 review (Figure 1) based on a data freeze from two months earlier at a total enrollment of 2,976 indicated persistence of the previously noted country-specific differences in baseline characteristics and event rates. Adverse events and SAEs by country again did not reveal patterns of concern. New U.S. sites were still being added in order to complete the trial on schedule.

On the September, 2011 monthly safety report the DSMB Chair detected a possible meaningful increase in the study drug permanent discontinuation rate in the masked arm (Arm X) that also had excess hyperkalemia and renal dysfunction. The Arm X discontinuation rate had become 22% compared to 15 % in Arm Y; the respective Arm X/Y rates had been 17%/12% in April 2010 and 7%/4% in January 2008. The DSMB Chair requested that the Executive Secretary communicate this information to the entire DSMB, and it was decided to closely monitor the situation with a rate rising to >25% in one arm being the level requiring further action. The rate remained below 25% in arm X until the end of the trial, and for example was 23% in May, 2012 three months after the last patient was enrolled and at the time of the third interim analysis. However, at the end of the trial the permanent study drug permanent discontinuation rate was 34% in the spironolactone arm and 31% in the placebo arm (S2), indicating that study drug withdrawals had increased towards the end of the trial.

At the December 2011 review (Figure 1) the Trial was at 94% of enrollment goal, with the U.S. continuing in the lead recruitment (n = 1,108 vs. 1,039 Russia), with all previously noted data patterns

unchanged. At this meeting the Trial leadership also presented data that the baseline characteristics of the TOPCAT current entire cohort were similar to other HFpEF trials.

DSMB meetings and data reviews for 2012 and 2013 are described in the main paper.

References

S1. Emerson M. Post-Mortem on Europe's First War of the 21st century (pdf). Centre for European Policy Studies (August 2008).

Table S1. Results of the B-type natriuretic peptide (NP) Pilot Project, BNP or NT-proBNP results in pg/ml.

***Country/Region*, Group**	**# of Subjects**	**BNP ≥100, NT-proBNP ≥360**			**Median, pg/ml**	**Range, pg/ml**
U.S. and Canada		**Yes**	**No**	**% Yes**		
Eligible via Hosp (BNP)	137	124	13	91	332	4-2382
Eligible via Hosp (NT-proBNP)	42	39	3	93	887	43-7903
Eligible via Hosp, either NP	179	163	16	91	–	–
Eligible via BNP	245	245	0	100	223	100-2686
Eligible via NT-proBNP	103	103	0	100	901	360-3814
Total # of Subjects	527	–	–	–	–	–
Russia						
Eligible via Hosp (BNP)	22	15	7	68	168	8-2399
Eligible via Hosp (NT-proBNP)	94	38	56	40	233	13-3294
Eligible via Hosp, either NP	116	53	63	46*	–	–
Eligible via BNP	8	8	0	100	178	113-119
Eligible via NT-proBNP	38	38	0	100	920	382-3406
Total # of Subjects	162				–	–
Georgia						
Eligible via Hosp (BNP)	2	2	0	100	1015	958-1072
Eligible via Hosp (NT-proBNP)	12	3	9	25	164	20-1800
Eligible via Hosp, either NP	14	5	9	36*	–	–
Eligible via BNP	8	8	0	100	450	129-913
Eligible via NT-proBNP	45	45	0	100	1572	393-15394
Total # of Subjects	67	–	–	–	–	–
Russia and Georgia Combined						
Eligible via Hosp (BNP)	24	17	7	71	217	8-2399
Eligible via Hosp (NT-proBNP)	106	41	65	39	208	13-3294
Eligible via Hosp, either NP	130	58	72	45*	–	–
Eligible via BNP	16	16	0	100	211	113-913
Eligible via NT-proBNP	83	83	0	100	1175	382-15394
Total # of Subjects	229	–	–	–	–	–

Hosp = heart failure hospitalization entry criterion; *p <0.001 (Bonferroni critical value = 0.0167) vs. U.S./Canada, Eligible via Hosp, either NP