



BeyondSpring Announces Positive Topline Results from its PROTECTIVE-2 Phase 3 Registrational Trial of Plinabulin in Combination with Pegfilgrastim for Prevention of Chemotherapy-Induced Neutropenia

- *Study met primary endpoint showing statistically significant improvement in rate of prevention of Grade 4 neutropenia in Cycle 1, $p=0.0015$*
- *Study met statistically significant improvement in key secondary endpoints, including DSN Cycle 1 D1-8, DSN Cycle 1, and Mean ANC Nadir Cycle 1*
- *Plinabulin in combination with pegfilgrastim, a Breakthrough Designation therapy, is believed to be the first product candidate to show improvement over standard of care (G-CSF monotherapy) for chemotherapy-induced neutropenia (CIN), a complication which affects as many as 440,000 chemotherapy patients in the U.S. annually*
- *Conference call and webcast to discuss results will be held today at 8:30 a.m. ET*

NEW YORK, November 16, 2020 (GLOBE NEWSWIRE) -- BeyondSpring (the "Company" or "BeyondSpring") (NASDAQ: BYSI), a global biopharmaceutical company focused on the development of innovative cancer therapies, today announced positive topline data from its PROTECTIVE-2 Phase 3 registrational study showing that plinabulin in combination with pegfilgrastim met the primary endpoint with statistically significant improvement in the rate of prevention of Grade 4 neutropenia in Cycle 1 (31.5% vs 13.6%, $p=0.0015$), as well as achieving statistical significance in all key secondary endpoints, including duration of severe neutropenia (DSN) and absolute neutrophil count (ANC) nadir.

The PROTECTIVE-2 Phase 3 study is a double-blind, active-controlled, global study that enrolled a total of 221 patients. Patients in the trial were treated with docetaxel, doxorubicin and cyclophosphamide (TAC, Day 1 dose) in a 21-day cycle with plinabulin (40 mg, Day 1 dose) + pegfilgrastim (6 mg, Day 2 dose) versus a single dose of pegfilgrastim (6 mg, Day 2 dose). The primary efficacy endpoint was rate of prevention of Grade 4 neutropenia.

Plinabulin in combination with pegfilgrastim showed a statistically significant improvement compared to pegfilgrastim alone, with topline data summarized below. Data from all 221 patients were analyzed (combination arm $n=111$, pegfilgrastim arm $n=110$).

- Primary endpoint (Rate of prevention of Grade 4 neutropenia): 31.5% combo therapy vs. 13.6% pegfilgrastim monotherapy, 95% CI 17.90 (7.13, 28.66), $p = 0.0015$
- Key secondary endpoints:
 - o DSN Cycle 1 Day 1-8 (ANC $< 0.5 \times 10^9$ cells/L): $p = 0.0065$,
 - o DSN Cycle 1: $p = 0.03$
 - o Mean ANC nadir Cycle 1 ($\times 10^9$ cells/L): $p = 0.0002$
 - o Duration of profound neutropenia Cycle 1 (ANC $< 0.1 \times 10^9$ cells/L): $p = 0.0004$,



According to literature, profound neutropenia leads to 80% patient death in first week of infection¹, and 48% febrile neutropenia, or FN, and 50% infection².

- Safety data:
 - o Lower Grade 4 adverse event (AE) frequency (58.6%) for combination compared to 80.0% in pegfilgrastim monotherapy

“These data clearly demonstrate the potential for this combination to offer superior therapy compared to standard of care in the prevention of CIN,” said Douglas W. Blayney, M.D., Professor of Medicine at the Stanford University School of Medicine and the global principal investigator for plinabulin’s CIN studies. “With current therapy, Grade 4 neutropenia still occurs in more than 80% of patients after chemotherapy, primarily in Week 1 after chemotherapy, which increases Emergency Room visits and hospitalizations due to infection and febrile neutropenia. Grade 4 neutropenia is also associated with increased mortality and reduced long-term survival due to reduction, delay, or interruption of chemotherapy. I would like to thank the participating patients, their families and the BeyondSpring team for their dedicated work to advance this combination therapy for the prevention of CIN in chemotherapy patients.”

Ramon Mohanlal, M.D., Ph.D., Chief Medical Officer and Executive Vice President of Research and Development at BeyondSpring noted, “We are pleased to have received Breakthrough Therapy designation from both the U.S. FDA and China NMPA for the plinabulin combination in CIN, underscoring the unmet medical need and potential benefit of the combination. We are working with regulatory agencies on the NDA submission, which is expected in Q1 2021 and have also begun preparation for commercialization. In addition to Plinabulin being developed as a treatment option for the prevention of CIN, it is also being investigated as a direct anticancer agent in a global Phase 3 trial of plinabulin + docetaxel for non-small cell lung cancer (NSCLC), with final data read-out in 1H 2021.”

Conference Call and Webcast Information

BeyondSpring’s management will host a conference call and webcast today at 8:30 a.m. Eastern Time. The dial-in numbers for the conference call are 1-877-451-6152 (U.S.) or 1-201-389-0879 (international). Please reference conference ID: 13713406. A live webcast will be available on BeyondSpring’s website at www.beyondspringpharma.com under “Events & Presentations” in the Investors section. An archived replay of the webcast will be available for 30 days.

1 Bodey et al. *Ann Intern Med* 64(2): 328 (1966); 2 Bodey et al. *Cancer* 41(4): 1610 (1978)

About Plinabulin in PROTECTIVE-2 (Study 106) CIN Study

The Phase 3 portion of PROTECTIVE-2 is a double-blind and active controlled global study. It was designed to evaluate the safety and efficacy in breast cancer, treated with docetaxel, doxorubicin and cyclophosphamide (TAC, Day 1 dose) in a 21-day cycle with plinabulin (40 mg, Day 1 dose) + Pegfilgrastim (6 mg, Day 2 dose) versus a single dose of Pegfilgrastim (6 mg, Day 2 dose). TAC is an example of high febrile neutropenia risk chemotherapy; all G-CSF biosimilar studies use TAC in the pivotal studies.



Plinabulin and G-CSFs such as Pegfilgrastim are believed to have complementary mechanisms in preventing chemotherapy-induced neutropenia (CIN). This is a superiority study in CIN efficacy in the rate of prevention of Grade 4 neutropenia, comparing the combination head-to-head against Pegfilgrastim alone. Literature shows that the Grade 4 neutropenia rate for TAC and Pegfilgrastim at 6 mg is 83 to 93 percent, which presents severe unmet medical needs.

The absolute neutrophil count (ANC) data, which are used to calculate these endpoints, were obtained through central laboratory assessments by Covance Bioanalytical Methods using standardized and validated analytical tests. Covance was the clinical contract research organization (CRO) for patient recruitment and monitoring of global sites for this study.

About Chemotherapy Induced Neutropenia (CIN)

Patients receiving chemotherapy typically develop CIN, a severe side effect that increases the risk of infection with fever (also called febrile neutropenia, or “FN”), which necessitates ER/hospital visits. The updated National Comprehensive Cancer Network (NCCN) guidelines expanded the use of prophylactic G-CSFs, such as Pegfilgrastim, from only high risk patients (chemo FN rate >20%) to intermediate risk patients (FN rate between 10-20%) to avoid hospital/ER visits during the COVID-19 pandemic. The revision of the NCCN guidelines effectively increases the addressable market of patients who may benefit from treatment with plinabulin, if approved, to approximately 440,000 cancer patients in the U.S. annually. Plinabulin is designed to provide protection against the occurrence of CIN and its clinical consequences in week 1, or early onset action after chemotherapy.

About Plinabulin

Plinabulin, BeyondSpring’s lead asset, is an investigational differentiated immune and stem cell modulator. Plinabulin is currently in late-stage clinical development to increase overall survival in cancer patients, as well as to alleviate CIN. Plinabulin had received Breakthrough Therapy Designation from China NMPA in CIN. The U.S. FDA granted Breakthrough Therapy designation to plinabulin for concurrent administration with myelosuppressive chemotherapeutic regimens in patients with non-myeloid malignancies for the prevention of chemotherapy-induced neutropenia (CIN). The durable anticancer benefits of plinabulin observed to date have been associated with its effect as a potent antigen-presenting cell (APC) inducer (through dendritic cell maturation) and T-cell activation (*Chem and Cell Reports*, 2019). Plinabulin’s CIN data highlight the ability to boost the number of hematopoietic stem / progenitor cells (HSPCs), or lineage-/cKit+/Sca1+ (LSK) cells in mice. Effects on HSPCs could explain the potential ability of plinabulin to not only treat CIN with a rapid onset, but also to reduce chemotherapy-induced thrombocytopenia and increase circulating CD34+ cells in patients.

Plinabulin currently is in an Expanded Access Program in the U.S.



About BeyondSpring

BeyondSpring is a global, clinical-stage biopharmaceutical company focused on the development of innovative cancer therapies. BeyondSpring's lead asset, plinabulin, a first-in-class agent as an immune and stem cell modulator, is in a Phase 3 global clinical trial as a direct anticancer agent in the treatment of non-small cell lung cancer (NSCLC) and Phase 3 clinical programs in the prevention of CIN. BeyondSpring has strong R&D capabilities with a robust pipeline in addition to plinabulin, including three immuno-oncology assets and a drug discovery platform using the protein degradation pathway, which is being developed in a subsidiary company, Seed Therapeutics, Inc. The Company also has a seasoned management team with many years of experience bringing drugs to the global market. BeyondSpring is headquartered in New York City.

Cautionary Note Regarding Forward-Looking Statements

This press release includes forward-looking statements that are not historical facts. Words such as "will," "expect," "anticipate," "plan," "believe," "design," "may," "future," "estimate," "predict," "objective," "goal," or variations thereof and variations of such words and similar expressions are intended to identify such forward-looking statements. Forward-looking statements are based on BeyondSpring's current knowledge and its present beliefs and expectations regarding possible future events and are subject to risks, uncertainties and assumptions. Actual results and the timing of events could differ materially from those anticipated in these forward-looking statements as a result of several factors including, but not limited to, difficulties raising the anticipated amount needed to finance the Company's future operations on terms acceptable to the Company, if at all, unexpected results of clinical trials, delays or denial in regulatory approval process, results that do not meet our expectations regarding the potential safety, the ultimate efficacy or clinical utility of our product candidates, increased competition in the market, and other risks described in BeyondSpring's most recent Form 20-F on file with the U.S. Securities and Exchange Commission. All forward-looking statements made herein speak only as of the date of this release and BeyondSpring undertakes no obligation to update publicly such forward-looking statements to reflect subsequent events or circumstances, except as otherwise required by law.

Investor Contact:

Ashley R. Robinson
LifeSci Advisors, LLC
+1 617-430-7577
arr@lifesciadvisors.com

Media Contact:

Darren Opland, Ph.D.
LifeSci Communications
+1 646-627-8387
darren@lifescicomms.com
