Filanesib (ARRY-520) is a highly selective, targeted inhibitor of kinesin spindle protein (KSP). KSP is a microtubule motor protein critical to the function of proliferating cancer cells. Filanesib inhibits a novel mechanism of action in the treatment of patients with multiple myeloma (MM). Patients who received filanesib in combination with bortezomib (BTZ) and dexamethasone (dex) were observed to have a low incidence of neuropathy.

Study Design and Objectives

- **Primary Objectives**
  - Dose escalation (esc): Determine the safety and maximum tolerated dose of filanesib when combined with BTZ plus low-dose dex
  - Expansion (exp): To obtain preliminary estimates of the efficacy of filanesib when combined with BTZ plus dex as determined by response rate

- **Study Design**
  - Open-label, multicenter, dose-escalation study to assess the safety of filanesib (IV) given with BTZ (IV or subcutaneous) and dex
  - 3 + 3 dose escalation followed by enrollment of expansion cohorts

- **Increasing doses of filanesib and BTZ without or with dex given in 28-day cycles in 2 dose schedules**

### Schedule 1:

- 77% Disease Control Rate (N=22)
  - 5 patients ongoing at data cutoff, of whom 4 PR
  - 1 sCR, 1 VPGR, 8 PR, 3 MR, 4 SD ≥ 8 weeks: 46% overall response rate (ORR; ≥PR), 59% clinical benefit rate (CBR; ≥MR)
  - In 11 patients who were previously BTZ-sensitive or naïve - 1 sCR, 1 VPGR, 5 PR, 5 MR and 2 SD ≥ 8 weeks (58% ORR, 83% CBR)
  - In 10 patients with PI-refractory (BTZ and/or carfilzomib) disease: 3 PR, 2 SD ≥ 8 weeks (30% ORR)

### Schedule 2:

- 67% Disease Control Rate (N=15)
  - 15 patients (10 dose escalation, 5 expansion) received filanesib 2.25 mg/m² or 3.0 mg/m² with 1.3 mg/m² weekly BTZ + dex for at least 2 cycles
  - 6 patients ongoing at data cutoff, of whom 2 have not yet had a response ≥PR
  - 1 sCR, 1 VPGR, 3 PR, 1 MR, 5 SD ≥ 8 weeks: 27% ORR, 33% CBR
  - In 11 patients who were previously BTZ-sensitive or naïve - 1 VPGR, 3 PR, 1 MR, 2 SD ≥ 8 weeks (36% ORR, 45% CBR)
  - In 4 patients with PI-refractory (BTZ and/or carfilzomib) disease: 3 SD ≥ 8 weeks

### Patient Characteristics

- **Key Inclusion Criteria**
  - Confirmed RRMM or plasma cell leukemia
  - RRMM defined as disease that progressed during or after last regimen
  - Dose escalation (esc): 2 + 2 prior treatment regimens
  - At least one prior full cycle of a proteasome inhibitor and an IMiD
  - Expansion (exp): 1 or 3 prior treatment regimens
  - BTZ naïve or sensitive
  - At least one prior full cycle of an IMiD
  - Measurable disease by SFE, UPEP, or PC
  - ECOG Performance Status 0 to 1
  - Adequate hematologic, hepatic and renal function
  - No ≥ Grade 2 neuropathy or any neuropathy with pain

### Safety

- **Maximum Planned Dose (MPD) Reached in Both Schedules**
  - Schedule 1: 1.5 mg/m² filanesib (D1,2,15) + 1.3 mg/m² BTZ (D1,8,15) + low-dose dex (D1,8,15) with prophylactic G-CSF
  - Schedule 2: 3.0 mg/m² filanesib (D1,15) + 1.3 mg/m² BTZ (D1,8,15) + low-dose dex (D1,8,15) with prophylactic G-CSF
  - These are the maximum single-agent doses of filanesib and BTZ and represent the recommended Phase 2 dose (RP2D). An RP2D and schedule will be chosen once the expansion cohorts are fully enrolled and analyzed.

- **Filanesib + BTZ Demonstrated an Acceptable Safety Profile**
  - Hematologic toxicity was the most commonly observed adverse event
  - 87% patients (22) at all dose levels with Grade 4 neutropenia when given prophylactic G-CSF
  - Of those 8 patients, 3 had associated SAEs (febrile neutropenia, pneumonia, abscess)
  - Neutropenia and thrombocytopenia have been reversible and non-cumulative
  - Low incidence of Grade 3/4 non-hematologic toxicity
  - 5/37 (14%) patients experienced neutropathy (Grade 2/3) with full dose BTZ
  - 6/37 (16%) patients required a dose reduction in filanesib due to an adverse event, regardless of causality
  - 5/37 (14%) patients discontinued treatment with filanesib due to an adverse event, regardless of causality
  - 9/37 (24%) patients experienced any SAE, regardless of causality or grade
  - A total of 8 treatment-related SAEs occurred in 4 patients
  - One patient who received a suspected accidental overdose of filanesib had 5 treatment-related SAEs: Grade 5 septic shock, Grade 5 Stevens-Johnson syndrome, Grade 4 stomatitis, Grade 4 febrile neutropenia, and Grade 3 acute renal failure
  - Other treatment-related SAEs (Grade 3 febrile neutropenia, Grade 3 pneumonia, Grade 2 subcutaneous abscesses)
  - A total of 14 unrelated SAEs occurred in 7 patients: Grade 3 celiac disease, Grade 3 metastatic gastric carcinoma, Grade 3 RSV pneumonia, Grade 3 LUE abscess, Grade 3 fall (2 events in 2 different patients), Grade 3 pathologic fracture of humerus, Grade 3 worsening hypertension, Grade 4 spinal cord compression, Grade 3 cholecyctitis, Grade 2 pneumonia, Grade 3 acute abscess of face, Grade 4 hypercalcemia, and Grade 3 accidental overdose.

### Summary

- **A recommended Phase 2 dose for filanesib + BTZ/dex has been established for 2 different dose schedules of filanesib**
  - Safety profile comparable in regimens with/without dex (Schedule 1)
  - Expansion cohorts at the recommended Phase 2 dose for 2 different schedules continue to demonstrate tolerability in combination with G-CSF
  - Rapidly reversible, non-cumulative neutropenia was the most significant toxicity
  - G-CSF adequately manages neutropenia
  - Low incidence of non-hematologic AEs
  - Predominantly Grade 1/2
  - Low incidence of neuropathy

- **Filanesib + weekly BTZ/dex demonstrated activity in this study**
  - 45% ORR observed in patients dosed at ≥1.25 mg/m² filanesib in Schedule 1
  - 36% ORR in PI-refractory patients
  - 58% ORR (83% CBR) in BTZ-sensitive or naïve patients
  - 27% ORR observed in patients dosed at ≥2.25 mg/m² filanesib (minimum 2 cycles) in Schedule 2
  - 6 patients ongoing, 2 of whom have not yet had a response ≥PR
  - 75% DCR in 4 PI-refractory patients
  - 36% ORR (45% CBR) in 11 patients with BTZ-sensitive or naïve disease
  - Enrollment in the Schedule 1 and Schedule 2 expansion cohorts is continuing (planned N=21 in each)

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*Our thanks to the patients and their families for their participation in this study.*