Nilotinib AEs (adverse events) in CML population:

The percentages below were taken from a randomized trial of nilotinib 300mg BID in newly diagnosed Ph+ CML patients (N=279)—taken from the Tasigna 2017 package insert.

- The most common (>10%) non-hematologic adverse drug reactions were rash, pruritis, headache, nausea, fatigue, alopecia, myalgia, and upper abdominal pain.
- Constipation, diarrhea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral edema, vomiting, and asthenia were observed less commonly (≤10% and>5%). These have been of mild to moderate severity, manageable and generally did not require dose reduction.
- The most common hematologic adverse drug reactions (all grades) were myelosuppression including: thrombocytopenia (18%), neutropenia (15%) and anemia (8%).

Hematologic parameters	**All grades**	**Grade 3/4**
Thrombocytopenia	18	10
Neutropenia	15	12
Anemia	8	4
Biochemistry parameters		
Elevated lipase	28	9
Hyperglycemia	50	7
Hypophosphatemia		8
Elevated bilirubin (total)	59	4
Elevated ALT	72	4
Hyperkalemia		2
Hyponatremia		1
Hypokalemia		<1
Elevated AST	47	1
Decreased albumin		0
Hypocalcemia		<1
Elevated alkaline phosphatase		0
Elevated creatinine		0
Elevated total cholesterol	28	
Elevated triglycerides	12	
Skin and subcutaneous tissue disorders		
Rash	38	<1
Pruritus	21	<1
Alopecia	13	0
Dry Skin	12	0
Gastrointestinal disorders		
Nausea	22	2
Constipation	20	<1
Diarrhea	19	1
Vomiting	15	<1
Abdominal pain upper	18	1
Abdominal pain	15	2
Dyspepsia	10	0
Nervous system disorders		
Headache	32	3

Dizziness	12	<1
General disorders and administration site conditions		
Fatigue	23	1
Pyrexia	14	<1
Asthenia	14	<1
Peripheral edema	9	<1
Face edema	<1	0
Musculoskeletal and connective tissue disorders		
Myalgia	19	<1
Arthralgia	22	<1
Muscle spasms	12	0
Pain in extremity	15	<1
Back pain	19	1
Respiratory, thoracic and mediastinal disorders		
Cough	17	0
Oropharyngeal pain	12	0
Dyspnea	11	2
Infections and infestations		
Nasopharyngitis	27	0
Upper respiratory tract infection	17	<1
Influenza	13	0
Gastroenteritis	7	0
Eye disorders		
Eyelid edema	1	0
Psychiatric disorders		
Insomnia	11	0
Vascular disorders		
Hypertension	10	1

- NCI Common Terminology Criteria for Adverse Events
  Grade 1: mild AE, Grade 2 = moderate AE, Grade 3 = severe AE, Grade 4 = life-threatening or disabling AE, Grade 5 = death related AE
  e.g. thrombocytopenia grade 1 plts 75-100K, grade 2 plts 50-75K grade 3 is plts <25K-50K, grade 4 <25K plts

QTc prolongation:
- Increase in QTc greater than 60msec from baseline was observed in 1 participant (0.4%)
- No participants had an absolute QTc of greater than 500msec while on study drug

Cardiac and Arterial Vascular Occlusive Events occurred in 9.3%:
- Ischemic heart disease-related cardiac events 5.0%
- Peripheral arterial occlusive disease 3.6%
- Ischemic cerebrovascular events 1.4%

Severe (Grade 3 or 4) fluid retention occurred in 3.9%
- Effusions (pleural effusion, pericardial effusion, ascites) or Pulmonary edema 2.2% (0.7% grade 3 or 4)

Discontinuation due to adverse reaction, regardless of relationship with study drug, occurred in 10% of participants.

Sudden deaths have been reported in 0.3% of patients with CML treated with nilotinib in clinical studies of 5,661 patients. The relative early occurrence of some of these deaths relative to the initiation of nilotinib suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence.

Safety of nilotinib in Parkinson disease:

Based on a single, small, open label study where 12 patients were treated for 24 weeks. Information below is a summary of the data reported in that study including data presented in the supplementary materials presented on-line

There were three serious adverse events (SAEs):

- One participant in the 300mg nilotinib group was withdrawn at week 4 and diagnosed with myocardial infarct and left bundle block.
- One participant in the 300mg nilotinib group was hospitalized with urinary tract infection (UTI).
- One participant in the 150mg nilotinib group was hospitalized with pneumonia and UTI.

Suppl Table 1- Serious Adverse Events (SAEs) requiring hospitalization in all participants.

System Organ Class/Preferred Term	Number of affected participants N=12	Total number of events	Number of affected participants in 150mg group. N=5	Number of affected participants in 300mg group. N=7
Cardiac disorders	1	2	0	1
Moderate cardiac ischemia			0	1
Myocardial Infarct			0	1
Infections and infestations	2	3	1	1
Urinary tract infection			1	1
Pneumonia			1	

The spectrum of AEs reported in this small PD population included:

- Mild confusion and hallucinations as well as anxiety and agitation, not reported in CML cohorts.
- Transient QTc prolongation>450ms
- Participants in the 150mg group reported three UTIs, two cases of pneumonia, one cold virus, one mild back pain, one mild headache, one mild dysgraphia, one mild left foot drag, one mild confusion, one mild hallucination, one mild paranoia, one mild agitation, one moderate anxiety, one mild incontinence, one moderate itching and one skin irritation.

- Participants in the 300mg group reported one incident of blurry vision, one diarrhea, one nausea, one mild fatigue, two generalized weakness, three UTIs, one pneumonia, one weight loss, one tooth extraction, one dizziness, two mild hallucinations, one mild paranoia, one mild crying episode, one mild urinary urgency, one mild cough and one eczematous lesion.

Suppl Table 2- Non-Serious Adverse Events in all participants throughout the study

System Organ Class/Preferred Term	Number of affected participants N=12	Total number of events	Number of affected participants in 150mg group . N=5	Number of affected participants in 300mg group. N=7
Cardiac disorders	2	3	1	1
QTc prolongation			1	2
Eye disorders	1	1	0	1
Mild blurry vision			0	1
Gastrointestinal disorders	2	2	0	2
Diarrhea				1
Nausea				1
General disorders	3	3	0	3
Mild fatigue			0	1
Generalized weakness			0	2
Infections and infestations	8	10	4	4
Urinary tract infection			3	3
Pneumonia			2	1
Cold virus			1	
Metabolism and nutrition disorders	1	1	0	1
Mild weight loss				1
Musculoskeletal and connective tissue disorders	2	2	1	1
Mild back pain			1	
Tooth extraction				1
Nervous system disorders	3	5	2	1
Mild headache			1	
Mild dysphragia			1	
Mild left foot drag			1	
Mild confusion			1	
Dizziness				1
Psychiatric disorders	4	8	3	1
Mild hallucinations			1	2
Mild Paranoia			1	1
Mild crying episodes				1
Mild agitation			1	
Moderate anxiety			1	
Renal and urinary disorders	2	2	1	1
Mild urinary urgency				1
Mild incontinence			1	
Respiratory, thoracic and mediastinal disorders	1	1	0	1
Mild cough				1
Skin and subcutaneous tissue disorders	2	3	1	1
Moderate itching			1	
Moderate skin irritation			1	
Mild eczematous lesions				1

Laboratory AEs in PD study:

- Three AEs below normal range of ALT level (<100%) were observed in the 150mg group.

- Two AEs above normal range (>100%), including one ALT and one bilirubin elevations were observed in the 150mg group.
- Two AEs with transient increase of ALT and one AST above normal range (>100%) were observed in the 300mg group but returned to normal by end of the study.

Take home points:

- Limited data
- Our study is using much lower doses of nilotinib than CML studies and once instead of twice daily administration
- Our population should be at lower risk of hematological AEs
- We have instituted comprehensive AEs monitoring
- Safety and tolerability are the primary outcome measures of our study
- The study safety data will be closely monitored by the Independent Data Safety Monitoring Board (DSMB) comprised of experts in PD, hematology and oncology
- Vigilance is necessary