ASP6294
NON-CONFIDENTIAL SUMMARY

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ASP6294: EXECUTIVE SUMMARY

- **ASP6294 is pegylated Fab fragment (no Fc portion), different compared to anti NGF mAb class,**
- **ASP6294 binds NGF, but does not form immune complex**
  - Pre-clinical evidence of reduced risk of inflammatory processes, of joint swelling and joint destruction
  - Theoretical advantage of reduced microvasculature inflammation and lower incidence or severity of abnormal peripheral nerve sensations, currently unproven preclinical or clinical mechanism
- **ASP6294 does not pass the placenta (no abnormalities found in reprotox study)**
- **Overall ASP6294 is well tolerated and safe in P1 and P2a study**
- **Simulation suggests ASP6294 320 mg Q4wk leads to further reductions in free NGF compared to Tanezumab 20 mg Q8wk dose**

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ASP6294 PROJECT CHARACTERISTICS

ASP6294 is a human monoclonal antibody consisting of a PEGylated nerve growth factor (NGF) binding Fab fragment

Mechanism of Action: Neutralization of nerve growth factor (NGF)

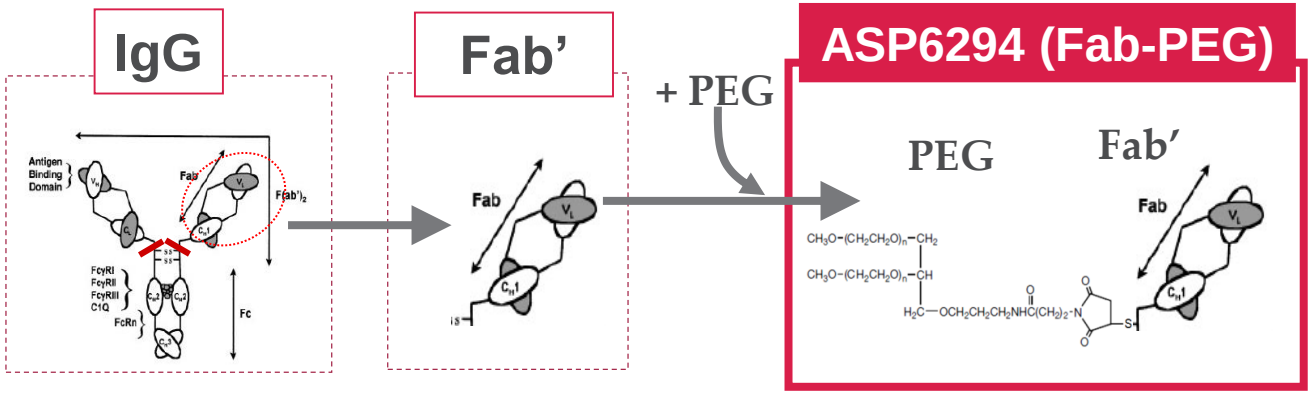
Formulation: Subcutaneous injection

Estimated patent term: 2032 + α (α = max 5 years)

Development phase:

Phase1 study(Completed), Phase 2 (Bladder Pain Syndrome/Interstitial Cystitis(BPS/IC) (Completed) => PJ terminated

ASP6294: BASIC FEATURES
FAB-PEG MODIFIED ANTI-NGF ANTIBODY



- High affinity
- High selectivity
- Very long $T_{1/2}$
- High BA even with sc (~ 80%)
- No CNS penetration
- No oral administration
- High CoG
- Immunogenicity
- Basically, no margin between target efficacy and MoA-associated side effects
- No penetration into cells

Antibody drugs

No Fc region (Monovalent antibody)

- Low or no risk of teratogenicity (very low placental transfer)
- No formation of large immune complex and associated side effects

PEGylation

Possibility of low immunogenicity (low risk of ADA formation)

BACKGROUND - ASP6294 ASSET

- **OA was the original target as an A6294 project, but placed on hold when the anti-NGF class was put on clinical hold by the FDA**
- **Binding affinity to NGF is similar between Tanezumab and ASP6294.**
- **ASP6294 is pegylated Fab fragment (no Fc portion), different compared to anti NGF mAb class,**
- **ASP6294 binds NGF, but does not form immune complex**
  - Pre-clinical evidence of reduced risk of inflammatory processes, of joint swelling and joint destruction
  - Theoretical advantage of reduced microvasculature inflammation and lower incidence or severity of abnormal peripheral nerve sensations, currently unproven preclinical or clinical mechanism
- **ASP6294 does not pass the placenta (no abnormalities found in reprotox study)**

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POC STUDY 6294-CL-0101

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, PROOF OF CONCEPT STUDY TO INVESTIGATE EFFICACY, SAFETY, PHARMACODYNAMICS AND PHARMACOKINETICS OF ASP6294 IN THE TREATMENT OF FEMALE SUBJECTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS.

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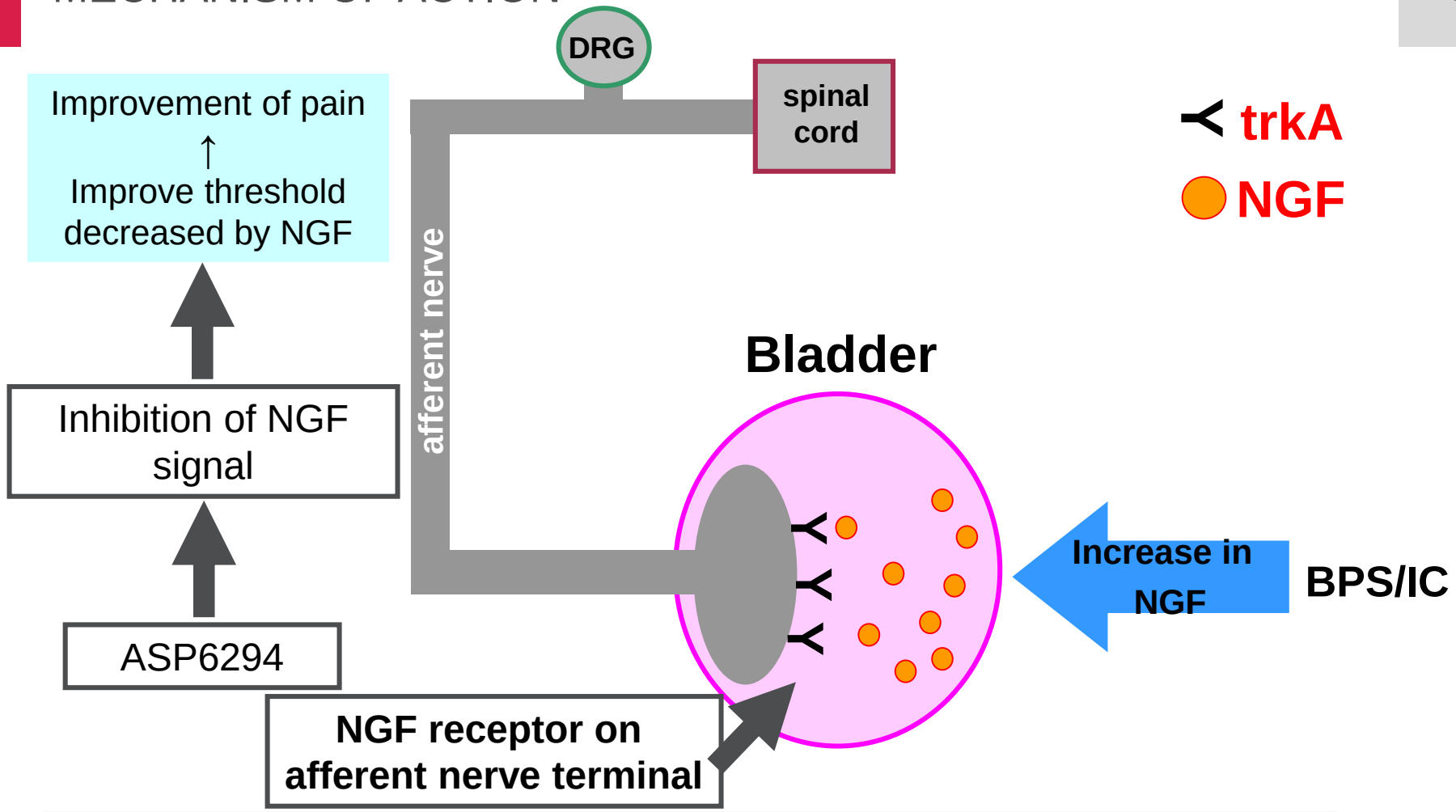
MECHANISM OF ACTION



NGF inhibition improves the decreased afferent nerve threshold. ASP6294 is expected to improve pain in patients with BPS/IC.

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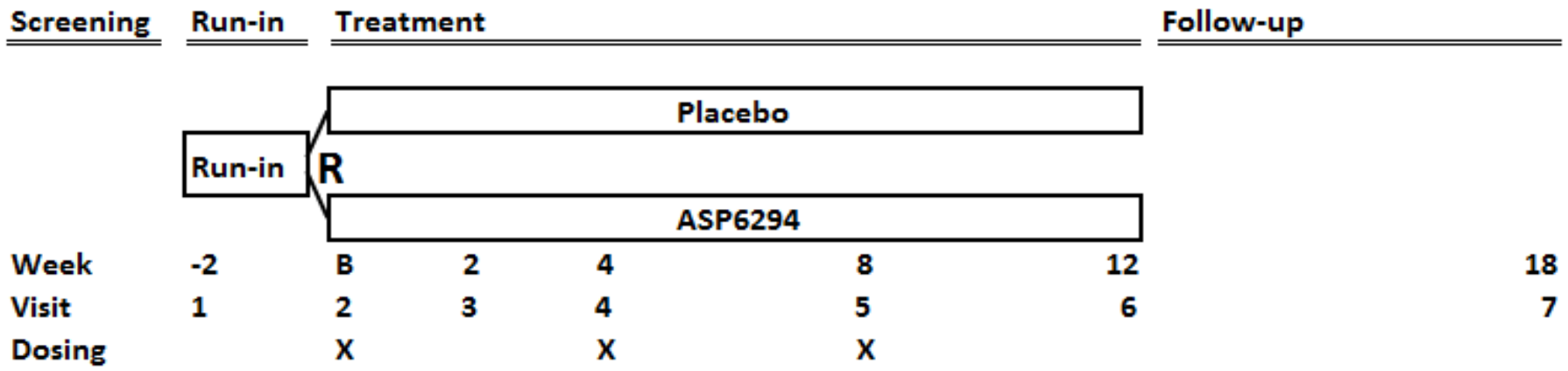
POC STUDY - OVERVIEW

POC study in female subjects at least 18 years of age diagnosed with BPS/IC according to the International Society for the study of BPS/IC (ESSIC) definition
(main patient selection criteria in backup slides)

Treatment randomization: 320 mg S.C. ASP6294 vs Placebo (1 : 1)

Total of 102 (FAS; LOCF) patients following a randomization of 114 patients
(based on expected effect size average MDP [primary EP] of 1.1 with a SD of 2.2)

Phases: 2 weeks run-in period, 12 weeks treatment period, 6 weeks follow-up period



POC STUDY - ENDPOINTS

Primary endpoint

- **CFB* average mean daily pain (MDP) at Visit 6/ Week 12**

Secondary endpoints

- **CFB average worst daily pain (WDP) at Visit 6/ Week 12**
- **CFB mean voiding frequency (VF) at Visit 6/ Week 12**
- **CFB mean number of level 3 or 4 urgency episodes per 24 hours (using the Patient Perception of Intensity of Urgency Scale [PPIUS]) at Visit 6/ Week 12**
- **Assessment of the Global Response Assessment (GRA) at Visit 5/ Week 8 and Visit 6/ Week 12**
- **CFB Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) at Visit 6/ Week 12**

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* CFB: change from baseline

POC STUDY - DOSE RATIONALE

Dose rationale

- **Dose of 600 mg i.v. highest dose tested in phase 1 and well tolerated; no MTD**
- **Dose levels of 100 and 320 mg s.c. also well tolerated; no MTD; 84% BA**
- **Interim PK/PD modeling showed that a dose of 320 mg s.c. is needed to reduce free NGF below 13% (of baseline) during at least 4 weeks.**
  Furthermore, injecting s.c. 320 mg is maximally feasible
  by 4 injections of 2 mL each per dosing (= 8 mL x 40 mg/ml = 320 mg)

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EFFICACY RESULTS(1)
PRIMARY EFFICACY ENDPOINT

Change from baseline data in average MDP at Week 12.

The upper bound of 90% confidence interval (CI) for the difference between ASP6294 and placebo arm was not less than 0, indicating that there is no statistically significant difference between ASP6294 and placebo with respect to the change from baseline in average MDP at Week 12.

Analysis Set = FAS	Placebo (N=59)	ASP6294 (N=53)
n	52	48
Baseline mean (SD)	5.68 (1.29)	5.57 (0.94)
Mean (SD) Change from Baseline	-2.25 (1.97)	-2.34 (1.85)
Adjusted Mean (SE) Change from Baseline [1]	-2.13 (0.26)	-2.34 (0.28)
Adjusted Treatment Difference (ASP6294 – placebo) (SE) [2]		-0.20 (0.38)
90% CI for Difference		[-0.84, 0.43]
p-value		0.591

n: number of subjects with non-missing values at Week 12.
[1] negative result indicates an improvement (lower MDP at Week 12 as compared to baseline)
[2] negative result indicates a larger change from baseline in average MDP in ASP6294 treated subjects compared to placebo treated subjects
Source: Table 12.3.1.1

EFFICACY RESULTS(2)
SELECTED SECONDARY EFFICACY ENDPOINTS

The results of the analyses of selected secondary efficacy endpoints are displayed in Table 3. No statistically significant treatment differences were observed and results are consistent with the primary efficacy endpoint.

Analysis Set = FAS	Placebo (N=59)	ASP6294 (N=53)
Change from baseline in voiding frequency per 24h at Week 12		
n	39	41
Baseline Mean (SD)	13.42 (3.73)	13.49 (3.64)
Mean (SD) Change from Baseline	-1.97 (3.08)	-2.22 (2.80)
Adjusted Mean (SE) Change from Baseline [1]	-1.15 (0.64)	-2.16 (0.65)
Adjusted Treatment Difference (ASP6294 – placebo) (SE) [2]		-1.01 (0.91)
90% CI for Difference		[-2.54, 0.52]
p-value		0.272
Change from baseline in average WDP at Week 12		
n	52	48
Baseline Mean (SD)	7.11 (1.11)	7.04 (0.93)
Mean (SD) Change from Baseline	-2.46 (2.31)	-2.18 (2.14)
Adjusted Mean (SE) Change from Baseline [1]	-2.33 (0.30)	-2.22 (0.32)
Adjusted Treatment Difference (ASP6294 – placebo) (SE) [2]		0.10 (0.44)
90% CI for Difference		[-0.63, 0.84]
p-value		0.817

n: number of subjects with non-missing values at Week 12.
[1] negative result indicates an improvement (lower value at Week 12 as compared to baseline)
[2] negative result indicates a larger change from baseline in ASP6294 treated subjects compared to placebo treated subjects
Source: Tables 12.3.2.1, 12.3.7.1, 12.3.12.1, and 12.3.18.1.

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EFFICACY RESULTS(3)
SELECTED SECONDARY EFFICACY ENDPOINTS

The results of the analyses of selected secondary efficacy endpoints are displayed in Table 3. No statistically significant treatment differences were observed and results are consistent with the primary efficacy endpoint.

Analysis Set = FAS	Placebo (N=59)	ASP6294 (N=53)
Change from baseline in BPIC-SS total score at Week 12		
n	54	49
Baseline Mean (SD)	26.00 (4.15)	26.08 (5.23)
Mean (SD) Change from Baseline	-7.02 (8.31)	-7.18 (8.29)
Adjusted Mean (SE) Change from Baseline [1]	-7.16 (1.07)	-7.41 (1.13)
Adjusted Treatment Difference (ASP6294 – placebo) (SE) [2]		-0.25 (1.56)
90% CI for Difference		[-2.84, 2.33]
p-value		0.872
Subjects with Moderately Improved or Better Grade on the GRA at Week 12		
Adjusted Percentage of Subjects with Successful GRA Response [3]	32.9%	40.6%
90% CI	(23.3%, 44.3%)	(29.6%, 52.7%)
Odds Ratio		1.394
90% CI		(0.702, 2.767)
p-value		0.426

n: number of subjects with non-missing values at Week 12.

[3] successful GRA response is defined as scores “moderately improved” or “markedly improved”.

Source: Tables 12.3.2.1, 12.3.7.1, 12.3.12.1, and 12.3.18.1.

SAFETY RESULTS : ADVERSE EVENTS (1)

TEAEs (MedDRA v18.1) : *M*ost common TEAEs occurring in at least 5% of patients in any treatment group. Five Serious TEAEs were reported in 3 subjects: 3 of 61 subjects (4.9%) in the placebo group, 0 of 56 subjects in the ASP6294 group.

Analysis Set = SAF	Placebo (N = 61) n (%)	ASP6294 (N = 56) n (%)
Overview		
TEAE	24 (39.3%)	29 (51.8%)
Drug-Related TEAE	9 (14.8%)	12 (21.4%)
Serious TEAE	3 (4.9%)	0
Drug-Related Serious TEAE	1 (1.6%)	0
TEAE Leading to Permanent Discontinuation of Study Drug	1 (1.6%)	1 (1.8%)
Death	0	0
Most common TEAEs (occurring in >=5% of subjects in any treatment group) [1]		
Headache	2 (3.3%)	5 (8.9%)
Arthralgia	2 (3.3%)	4 (7.1%)
Nasopharyngitis	1 (1.6%)	3 (5.4%)

Number of subjects and percentage of subjects (%) are shown.
[1] Sorted by the incidence in ASP6294 group
Source: Tables 12.6.1.1 and 12.6.1.10

SAFETY RESULTS : ADVERSE EVENTS (2)

TEAEs of Special Interest (MedDRA v18.1) – SAF: All TEAEs of Special Interest in the ASP6294 group were related to study drug.

Category of TEAE of Special Interest Preferred Term	Placebo (N = 61) n (%)	ASP6294 (N = 56) n (%)
Overall	3 (4.9%)	7 (12.5%)
Arthralgia	2 (3.3%)	4 (7.1%)
Arthralgia	2 (3.3%)	4 (7.1%)
Pain in extremity events	0	3 (5.4%)
Myalgia	0	2 (3.6%)
Pain in extremity	0	2 (3.6%)
Peripheral edema	0	0
Peripheral sensory function abnormalities	1 (1.6%)	2 (3.6%)
Hyperaesthesia	0	1 (1.8%)
Paraesthesia	1 (1.6%)	1 (1.8%)

Number of subjects and percentage of subjects (%) are shown.
Source: Table 12.6.1.15
Subject 3710110005 in ASP6294 group had events of arthralgia, myalgia and pain in extremity.

OTHER SAFETY ASSESSMENTS

<u>Adjudicated Neurological TEAEs and Changes in Sensory Function Results:</u>
Adjudicated neurological TEAEs were reported for 7 subjects (4 in ASP6294 group and 3 in placebo group). Per review by the Independent Neurological Adjudication Committee, none of the events were related to neuropathy.

<u>Laboratory Tests of Special Interest</u>: For 4 subjects (3 in ASP6294 group and 1 in placebo group) a potentially clinically significant result was reported:

- **Total Bilirubin value > 1.5xULN (but <2xULN) was reported in 3 subjects (2 in ASP6294 and 1 in placebo), and**
- **Alkaline Phosphatase value >1.5xULN in 1 subject (1 in ASP6294 and 0 in placebo).**

TEAE COMPARISON IN BPS/IC POPULATION: ASP6294 VS TANEZUMAB

	# of Placebo (%)	# of Tanezumab (%)	# of Placebo (%)	# of ASP6294 (%)
TEAE	74 (71.2)	70 (67.3)	24 (39.3)	29 (51.8)
Serious TEAE	4 (3.8)	4 (3.8)	3 (4.9%)	0
Discontinued due to AEs	22 (21.2)	21 (20.2)	1 (1.6%)	1 (1.8%)
Headache	11 (10.6)	17 (16.3)	2 (3.3)	5 (8.9)
Injection site reaction	4 (3.8)	2 (1.9)	3 (4.9%)	0
TEAEs of Special Interest				
Arthralgia	4 (3.8)	14 (13.5)	2 (3.3)	4 (7.1)
Myalgia	1 (1.0)	6 (5.8)	0	2 (3.6)
Pain in extremity	3 (2.9)	10 (9.6)	0	2 (3.6)
Peripheral edema	1 (1.0)	4 (3.8)	0	0
Paresthesia	6 (5.8)	16 (15.4)	1 (1.6%)	1 (1.8%)
Hyperesthesia	0 (0.0)	8 (7.7)	0	1 (1.8%)
TEAEs of peripheral sensory function abnormalities				
Paresthesia	6 (5.8)	16 (15.4)	1 (1.6%)	1 (1.8%)
Hyperesthesia	0 (0.0)	8 (7.7)	0	1 (1.8%)
Allodynia	0 (0.0)	5 (4.8)	0	0
Hypoesthesia	1 (1.0)	2 (1.9)	0	0
Peripheral neuropathy	0 (0.0)	2 (1.9)	0	0
Dysesthesia	0 (0.0)	1 (1.0)	0	0
Peripheral motor neuropathy	0 (0.0)	1 (1.0)	0	0
Peripheral sensory neuropathy	0 (0.0)	1 (1.0)	0	0

Nickel JC et al. J Urol (2016) 195:942-948
(US, Canada, West and East EU, Russia, Japan)

B6294 _ Serenity Study
(West and East EU, Russia)

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PD SUMMARY

- The original exposure/NGF model was developed using ELISA assay results from P1 data
- Model was used to set PoC dose targeting >87% reduction in free NGF in 99% of subjects
- The model parameters in original model were tentatively modified to explain the observed POC results from LC-MS (Q2 assay) and the simulation was performed
- Simulation suggests ASP6294 320 mg Q4wk leads to further reductions in free NGF compared to Tanezumab 20 mg Q8wk dose

SUMMARY

Efficacy

No statistically significant treatment differences in primary and selected secondary efficacy endpoints were observed between ASP6294 and placebo.

Safety

Overall ASP6294 is well tolerated and safe in the BPS/IC population.

The percentage of subjects with TEAEs of special interest in ASP6294 group is slightly higher as compared to the placebo group. However, the overall percentage of subjects with TEAEs of special interest in ASP6294 group is considerably low.

None of the neurological TEAEs were adjudicated per Independent Neurological Adjudication Committee to be related to neuropathy.

PD

Simulation suggests ASP6294 320 mg Q4wk leads to further reductions in free NGF compared to Tanezumab 20 mg Q8wk dose

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STATUS AND OPPORTUNITY

- **TLR of POC study in BPS/IC was obtained in May 2019 but this result met No go criteria consistent with competitors failure in this indication. Astellas decided to terminate BPS/IC indication.**
  - No statistically significant treatment differences in primary and selected secondary efficacy endpoints were observed between ASP6294 and placebo.
  - Overall ASP6294 is well tolerated and safe in the BPS/IC population.
  - The percentage of subjects with TEAEs of special interest in ASP6294 group is slightly higher as compared to the placebo group. However, the overall percentage of subjects with TEAEs of special interest in ASP6294 group is considerably low.
  - **Other anti NGF antibodies, Tanezumab and Fulranumab as well as Aquinox also failed in larger clinical trials for BPS/IC.**
  - Team hypothesis that main reason for failure in BPS/IC study is due to highly heterogeneous patient population also suggested by competitors.
  - Tanezumab demonstrated efficacy in PDPN, CLBP, and OA despite failure in BPS/IC indication.
  - **Based on the favorable safety profile and efficacy demonstrated by this class for other pain indications, an opportunity potentially exists for ASP6294 in PDPN, CLBP, and OA.**