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Phase 2, Randomized, Double-Blind Trial of EC-18 to Alter the Severity and Course of Oral Mucositis Due to Chemoradiation for Head and Neck Cancer

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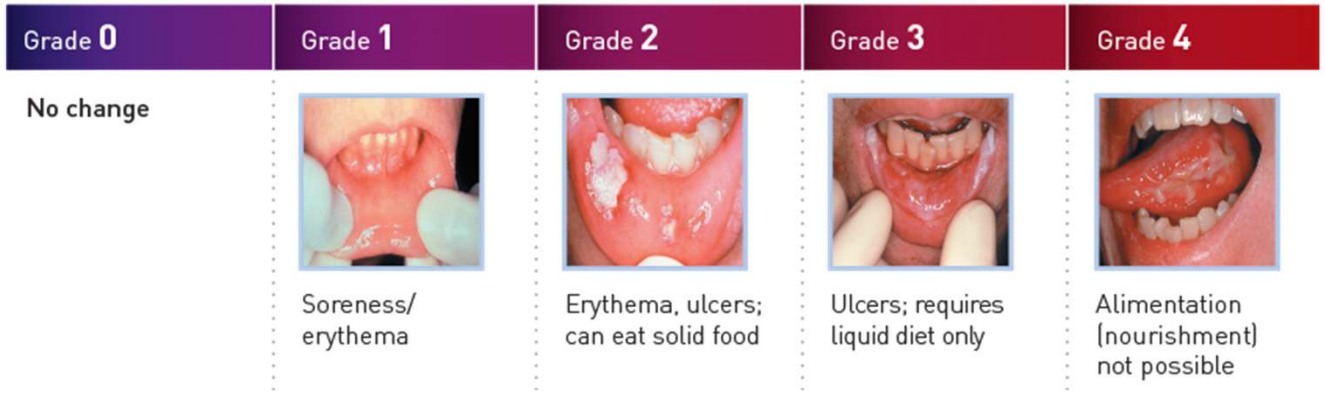
Disclosure

- Employed by the University of Oklahoma Health Stephenson Cancer Center
- Trial funding (NCT03200340) provided by Enzychem Lifesciences

- I have no financial disclosure or relevant conflicts of interest with the presented material

Oral Mucositis (OM)



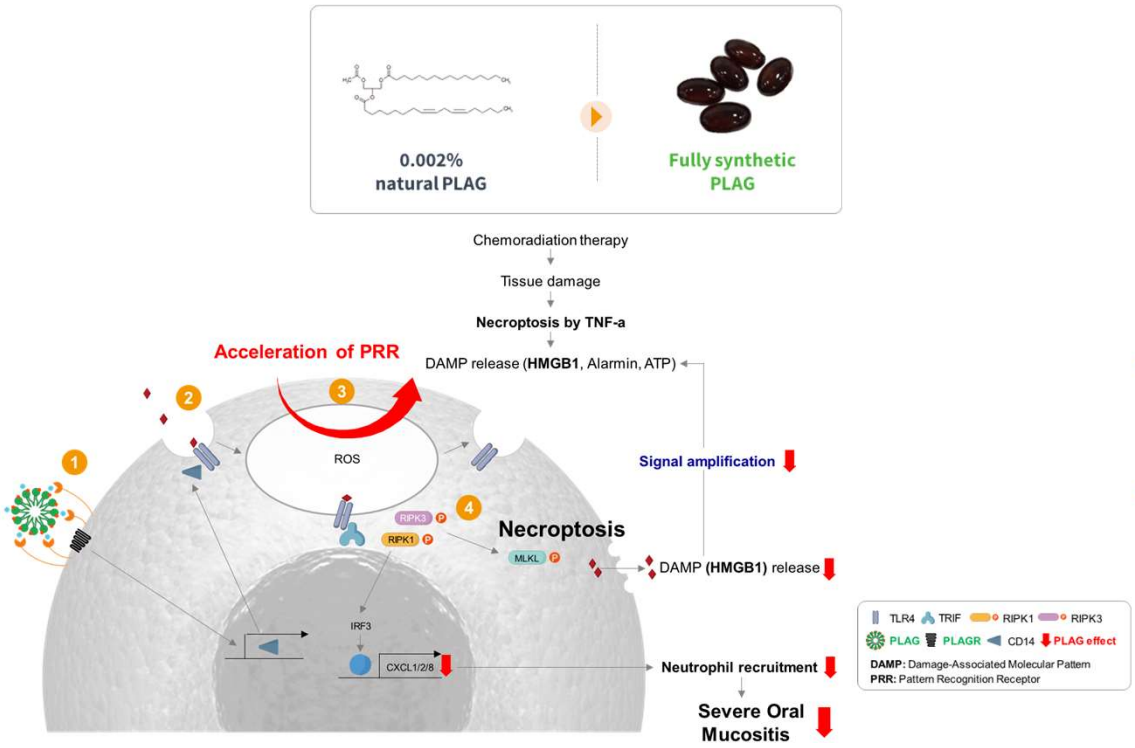
- Common and impactful toxicity of concomitant chemoradiation regimens used for the treatment of head and neck cancers – severe OM (SOM) in about 70% of patients
- Unmet clinical need contributes to adverse patient outcomes, treatment intolerance, and increased resource use
- Key pathobiological targets for mechanistically-based interventions include oxidative stress, the innate immune response, and pro-inflammatory initiators

www.myhealth.gov.my/en/oral-mucositis

SO3

Introduction

EC-18: Orally available, lipid-based small molecule



- Also known as 1-Palmitoyl-2-Linoleoyl-3-Acetyl-rac-Glycerol (PLAG)/Mosedipimod
- Each capsule contains 500 mg of active pharmaceutical ingredient (PLAG) and 1 mg of antioxidant (α-tocopherol)
- Excellent drug safety profile based on non-clinical and Phase 1 clinical studies
- EC-18 acts as an immune modulator contributing to rapid resolution of inflammation and fast return to immune homeostasis

Slide 5

JS0 How was EC-18 discovered?
Ji Sun, 2022-05-26T21:29:23.238

SO0 0 in 1989. the original researcher, Dr. Sanghee Kim, an oncologist, began investigating the effects of deer antler and discovered the fact that it stimulates the proliferation of hematopoietic stem cells from bone marrow.
Sookyung Oh, 2022-05-31T18:47:42.370

SO0 1 The research finally identified several elements of the monoacetyldiglycerides (MADG) family and proved that each of the elements stimulates hematopoietic stem cells. Upon the identification of the MADG and its chemical equation, Dr. Tae-Seok Lee of Enzychem came up with a method for its synthesis. Research has since been focused on the illumination of the biological functions of the MADG, especially MADG3, synthesized by Dr. Lee MADG3 came to be christened EC-18 later on.
Sookyung Oh, 2022-05-31T18:48:42.413

SO1 Is EC-18 a biological product?
Sookyung Oh, 2022-05-31T18:55:37.292

SO1 0 No, EC-18 is a fully synthesized lipid based small molecule.
Sookyung Oh, 2022-05-31T18:56:09.081

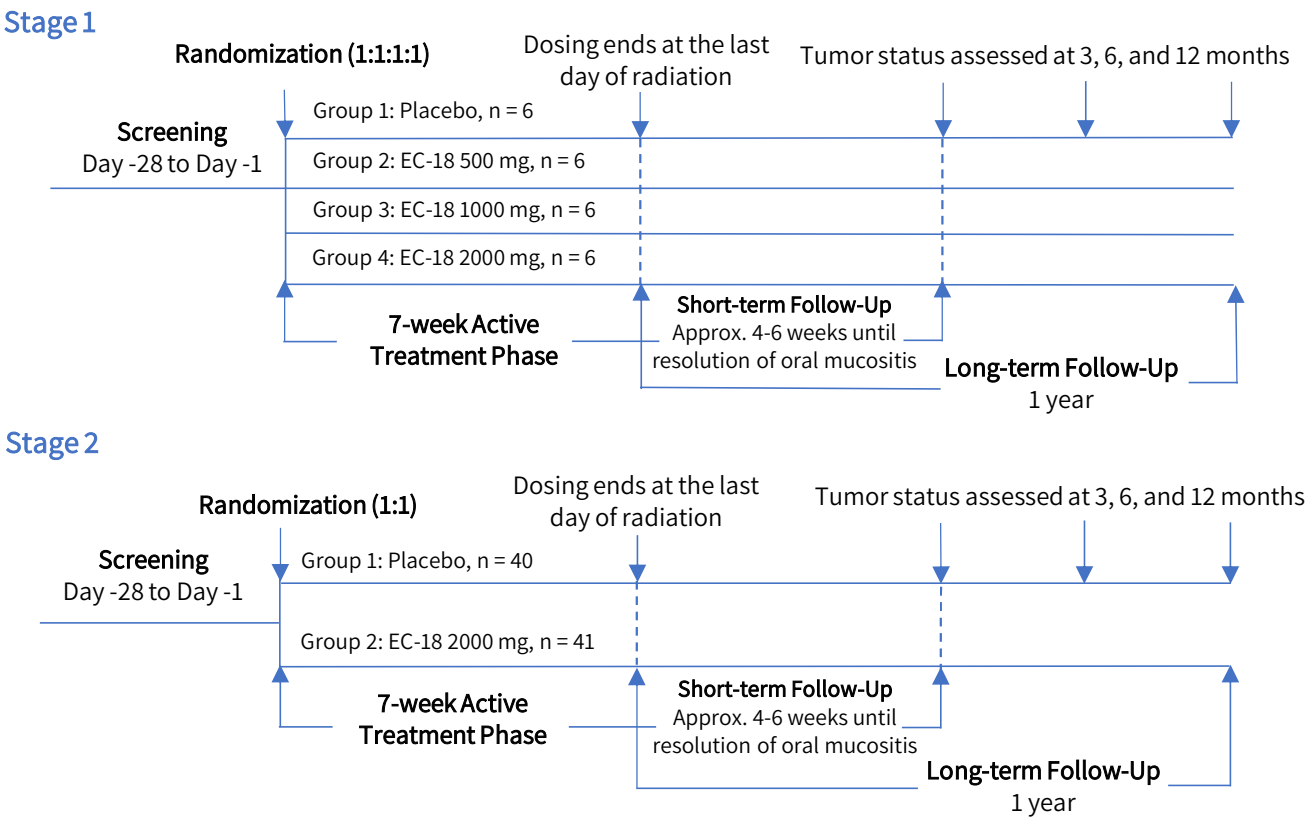
SO2 Where does EC-18 bind to?
Sookyung Oh, 2022-05-31T19:47:09.694

SO2 0 EC-18 binds to one of the GPCRs (G Protein coupled receptors).
Sookyung Oh, 2022-05-31T19:50:30.659

SO3 Is this an anti-inflammatory drug?
Sookyung Oh, 2022-05-31T19:47:22.957

SO3 0 Yes, our drug class belongs to anti-inflammatory agent.
Sookyung Oh, 2022-05-31T20:18:07.744

Study Design



JS4

Patient Population

- Squamous cell carcinoma of the mouth, oropharynx, hypopharynx, or nasopharynx
- IMRT + cisplatin
- ≥ 55Gy on ≥ 2 mucositis sites

KK1
KK0

Study Drug Treatment Regimen

- Administer two capsules twice a day for 7 weeks
- Start on the same day as the day of first radiation

Slide 6

KK0 Q: Did any of the patients have difficulty swallowing the capsules? How big is the capsule?
Koeun Kim, 2022-05-26T15:16:27.367

KK0 0 A: The capsules are about a size of a small pea. The patients with Grade 3 or higher had difficulties swallowing not only study drug but also any solid food. But we still encouraged our patients to take the study drug to reduce the potential incidence of severe oral mucositis.
Koeun Kim, 2022-05-26T15:20:20.749

KK1 Q: Did patients take EC-18 on days they didn't receive radiation?
Koeun Kim, 2022-05-26T15:17:46.799

KK1 0 A: Yes, the patients were told to take EC-18 every day for 49 days including the days they didn't receive radiation treatment (weekends and/or holiday(s)).
Koeun Kim, 2022-05-26T15:18:02.611

KK2 Q: Isn't 2000 mg per day too high of a dose?
Koeun Kim, 2022-05-26T15:19:12.793

SO2 0 A: Based on Phase 1 healthy volunteer study, EC-18 was well tolerated up to 4000 mg/day. In stage 1 of Phase 2 study, EC-18 2000 mg/day was show to be safe and well-tolerated.
Sookyung Oh, 2022-05-31T19:03:30.338

KK3 Q: Is it a prophylactic, prevention, or treatment?
Koeun Kim, 2022-05-26T15:32:50.140

SO3 0 A: None of the above. It is a supportive care study drug, which helps reduce the severity of Oral Mucositis.
Sookyung Oh, 2022-05-31T19:04:26.151

JS4 What is the half-life of EC-18? Can it be taken as QD instead of BID?
Ji Sun, 2022-05-26T21:30:32.036

SO4 0 A: Yes, in our other indications we allowed patients to take EC-18 once a day. However, we suggest patients to take twice a day since OM patients have difficulty swallowing.
Sookyung Oh, 2022-05-31T19:07:35.606

SO4 1 A: We'll get back to you on the half-life.
Sookyung Oh, 2022-05-31T19:08:02.200

Study Design (Cont'd)

Endpoints

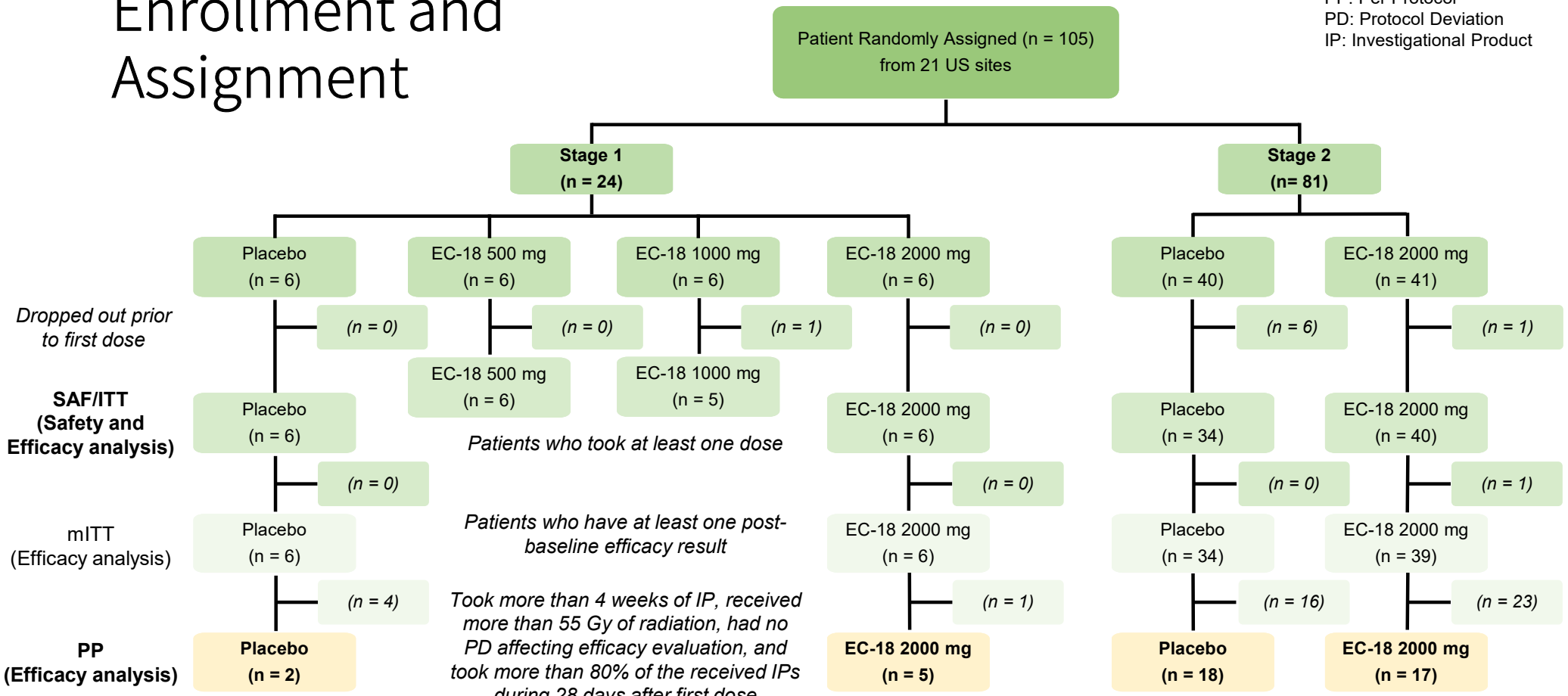
- Primary efficacy:
  - Duration of SOM during active and short-term follow-up (STFU)
- Secondary:
  - Incidence of SOM up to STFU
  - Time to SOM onset
  - Time to opioid use
- Safety:
  - Incidence of AEs and SAEs

Covariates

- Cisplatin regimen (Weekly vs. Tri-weekly)
- Human papillomavirus (HPV) status (positive vs. negative)

Enrollment and Assignment

SAF: Safety analysis set
ITT: Intent-to-treat
mITT: Modified intent-to-treat
PP: Per Protocol
PD: Protocol Deviation
IP: Investigational Product



Patient Baseline Characteristics

- Well balanced across two arms

Characteristics	No. (%) of Patients						Total (N = 97)
	Stage 1				Stage 2		
	Placebo (n = 6)	EC-18 500 mg (n = 6)	EC-18 1000 mg (n = 5)	EC-18 2000 mg (n = 6)	Placebo (n = 34)	EC-18 2000 mg (n = 40)	
Tumor Site							
Nasopharynx	0	1 (17)	0	0	1 (3)	0	2 (2)
Hypopharynx	0	0	0	0	0	1 (2)	1 (1)
Oropharynx	2 (33)	3 (50)	2 (40)	4 (67)	27 (79)	33 (83)	71 (73)
Oral Cavity	4 (67)	2 (33)	2 (40)	2 (33)	5 (15)	6 (15)	21 (22)
Multiple	0	0	1 (20)	0	0	0	1 (1)
Unknown	0	0	0	0	1 (3)	0	1 (1)
TNM Stage							
0-II	3 (6)	2 (4)	2 (4)	2 (4)	18 (53)	25 (53)	52 (54)
III	1 (5)	3 (15)	2 (10)	3 (15)	7 (21)	4 (10)	20 (20)
IV	2 (8)	1 (4)	1 (4)	1 (4)	9 (26)	11 (27)	25 (26)
Tumor HPV status							
Positive	4 (67)	5 (83)	3 (60)	6 (100)	22 (65)	28 (70)	68 (70)
Negative	2 (33)	1 (17)	0	0	9 (26)	9 (23)	21 (22)
Unknown	0	0	2 (40)	0	3 (9)	3 (7)	8 (8)
Cisplatin Schedule							
Every 3 weeks (High-dose)	5 (83)	0	2 (40)	1 (17)	14 (41)	12 (30)	34 (35)
Weekly (Low-dose)	1 (17)	6 (100)	3 (60)	5 (83)	20 (59)	28 (70)	63 (65)

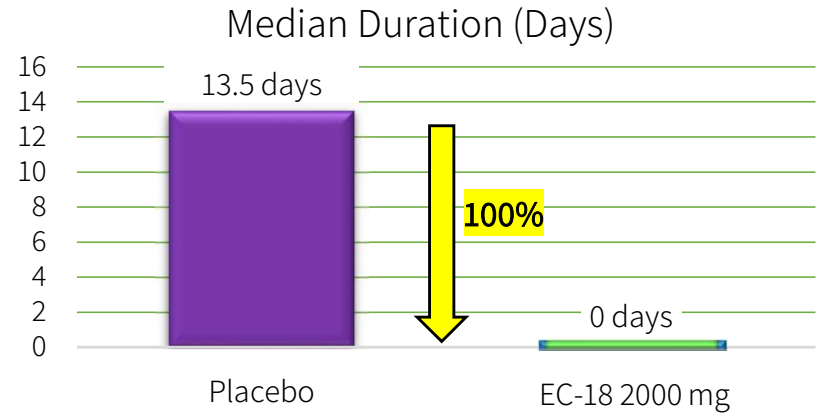
Efficacy Results

SO5

Duration and Incidence of SOM KK3

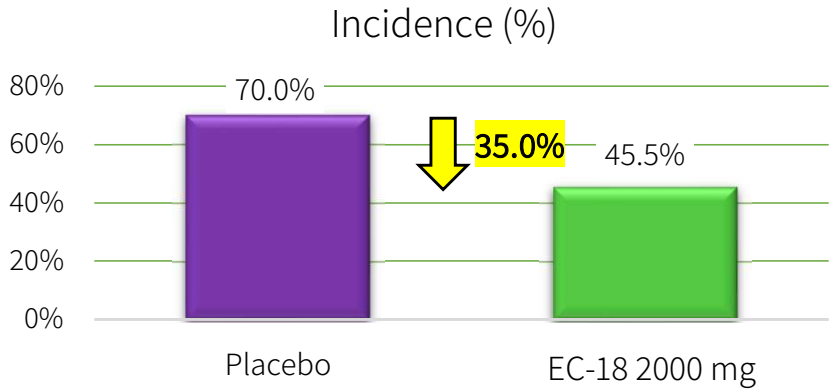
Duration of SOM Up to STFU Period (PP)

Duration (days)	Placebo	EC-18 2000 mg
n	20	22
Median	13.5	0.0
Min, Max	0, 77	0, 48



Incidence of SOM Up to STFU Period (PP)

Incidence [n(%)]	Placebo	EC-18 2000 mg
n	20	22
Incidence of SOM	14 (70.0)	10 (45.5)



Slide 11

KK0 Q: Did you get a statistical significance or p value with analysis of such a small number of patients?
Koeun Kim, 2022-05-26T15:00:11.886

SO0 0 A: Since this is a Phase 2 proof of concept study, we did not expect a strong statistical significance (our p=0.5575 for SOM duration; 0.1894 for SOM incidence). The signal we saw for the compliant patient group sufficient to the purpose of this study.
Sookyung Oh, 2022-05-27T15:51:27.103

KK1 Q: How are the results among patients who developed SOM? (Excluding ones who didn't develop SOM)
Koeun Kim, 2022-05-26T15:21:21.919

SO1 0 A: It is a little misleading to be looking at median duration for people who never developed SOM, but we do know that the time to onset of SOM for the EC-18 group was 8 days later than the placebo group.

FYI: Median duration of SOM only for patients who developed SOM was 23.0 vs 34.3 days (Placebo vs. EC-18) for up to STFU and 14.0 vs 13.0 days fo up to Active treatment period.
Sookyung Oh, 2022-05-27T15:55:48.729

KK2 Q: How do you score the days of SOM duration when you had an incidence of SOM? How is duration 0 days but still have and incidence rate of 45.5%?
Koeun Kim, 2022-05-26T15:22:16.887

SO2 0 A: This is because the duration is based on the imputed median value from all patients while incidence rate is based on the SOM occurrence.
Sookyung Oh, 2022-05-31T19:22:15.086

KK3 Q: What is your actual comparison to the standard of care (SOC)? Do you think that your placebo data is very close to SOC?
Koeun Kim, 2022-05-26T15:23:20.780

SO3 0 A: Our PP placebo duration was 13.5, which was smaller but comparable to the industry reported placebo duration.
Sookyung Oh, 2022-05-31T19:25:36.241

JS4 What was your mean of SOM duration?
Ji Sun, 2022-05-26T21:27:34.721

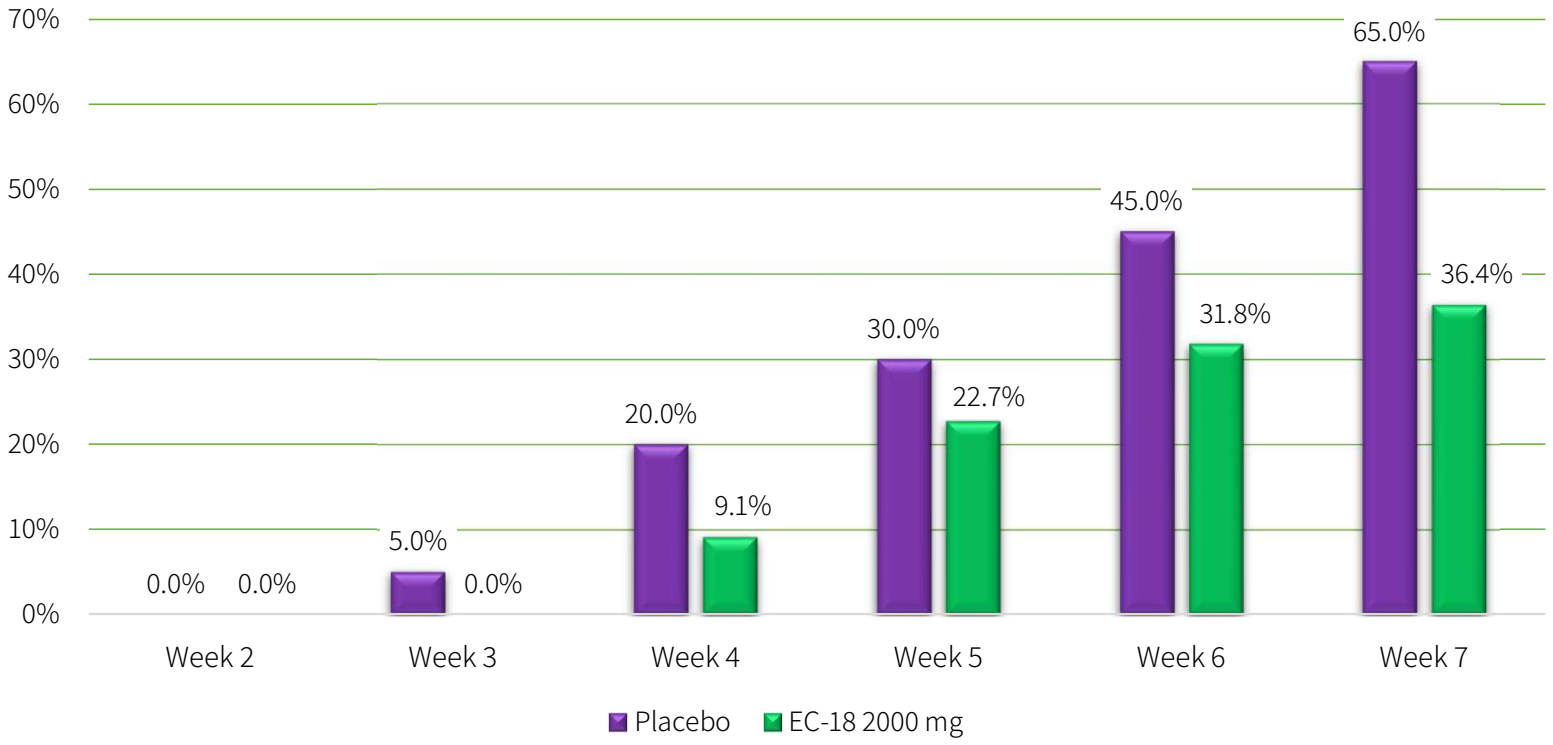
SO4 0 A: 19.3 vs. 15.3 days (Placebo vs. EC-18) for up to STFU and 9.3 vs 6.2 days for up to Active treatment period in PP population.
Sookyung Oh, 2022-05-27T16:01:11.741

SO5 What do your mITT/ITT results show?
Sookyung Oh, 2022-05-31T19:28:06.804

SO5 0 It is unfortunate that the half of mITT population were not compliant. We believe the results for the PP population (compliant group) truly represent the EC-18 efficacy.
Sookyung Oh, 2022-05-31T19:32:20.503

Cumulative SOM Incidence Over Time (PP) KK0

KK1



Slide 12

KK0 Q: Do you have data after Week 7? How are the results?
Koeun Kim, 2022-05-26T15:03:05.397

SO0 0 A: The cumulative SOM incidence at the end of Active treatment period is 65% for Placebo and 40.9% for EC-18, and the cumulative SOM incidence a
the end of STFU period is 70% for Placebo and 45.5% for EC-18
Sookyung Oh, 2022-05-27T17:25:56.217

KK1 Q: In the previous slide, the incidence reduction was 35%. How did the incidence drop 44% in Week 7?
Koeun Kim, 2022-05-26T15:06:43.202

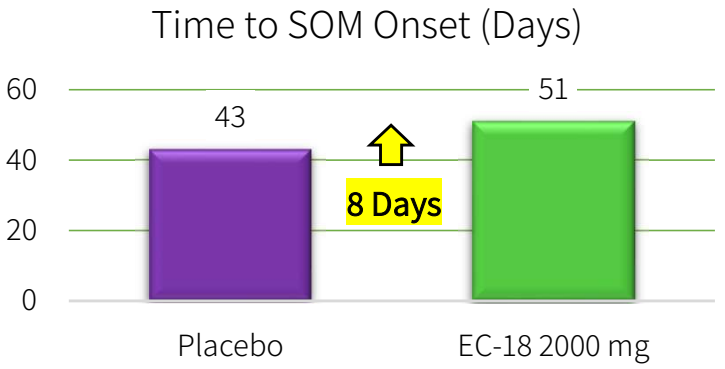
SO1 0 A: This graph shows the cumulative incidence up to 7th week, but our incidence results include Active treatment period, which can go beyond 7 weeks (up to 9 weeks).
Sookyung Oh, 2022-05-27T17:33:11.673

Secondary Endpoints

Time to SOM Onset (PP)

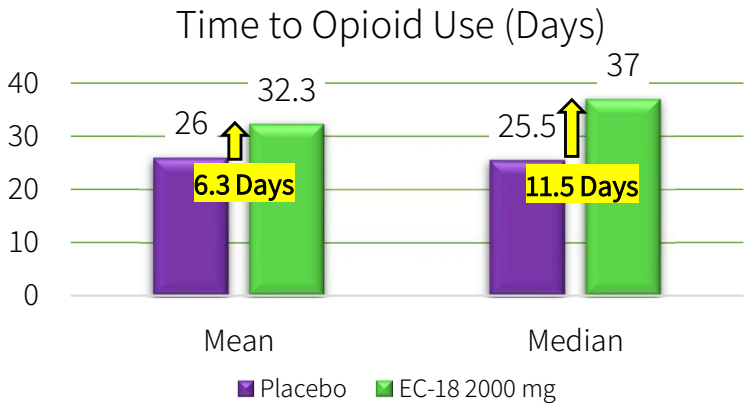
Time to onset of SOM (days; 95% CI)*	EC-18 2000 mg	Placebo
n	22	20
Median	51 (33.0,)	43 (28.0,)

*Kaplan-Meier Estimation



Time to Opioid Use (PP) KK0

Time to Opioid Use (days)	Placebo	EC-18 2000 mg
n	6	8
Mean	26	32.3
Median	25.5	37



Slide 13

KK0 Q: How was the duration of opioid use? Were patients on a shorter period of opioids?
Koeun Kim, 2022-05-26T15:07:23.119

SO0 0 A: Per secondary endpoint, we measured time of opioid use. Our data doesn't capture the end date of opioid use per each patient and therefore, we can't measure the opioid use duration,
Sookyung Oh, 2022-05-27T19:04:21.690

Covariate Analysis - Cisplatin Regimen and HPV Status

- EC-18 favorably impacted SOM incidence in patients:
  - With Weekly low-dose cisplatin
  - With HPV+ tumors

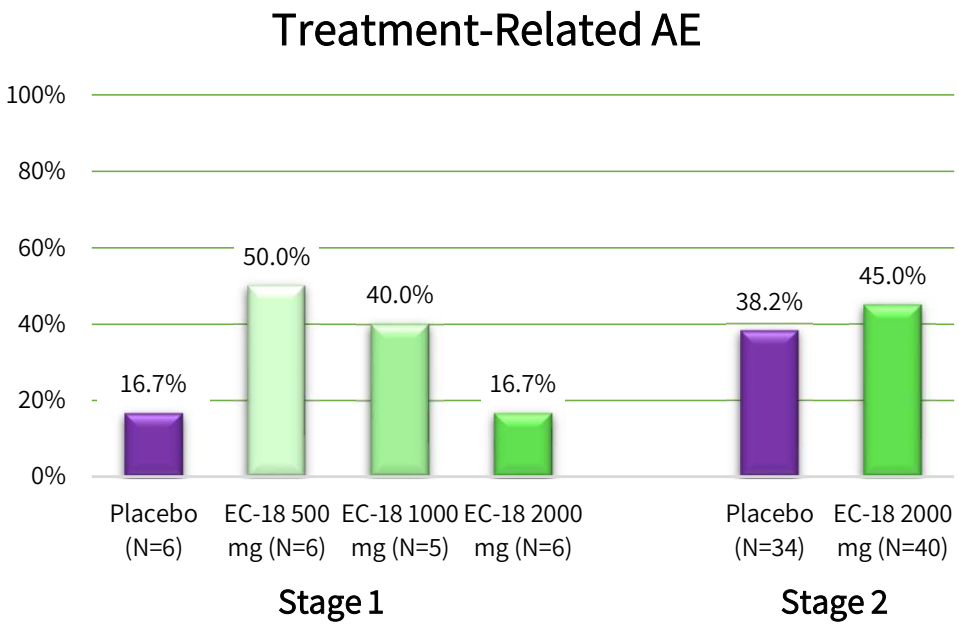
PP Subgroups	EC-18 2000mg (N=22)	Placebo (N=20)
All PP	45.5% (10/22)	70.0% (14/20)
Cisplatin (Weekly)	37.5% (6/16)	70.0% (7/10)
Tri-Weekly Cisplatin	66.7% (4/6)	70.0% (7/10)
HPV+	35.3 (6/17)*	66.7% (8/12)
HPV-	75.0% (3/4)	71.4% (5/7)*

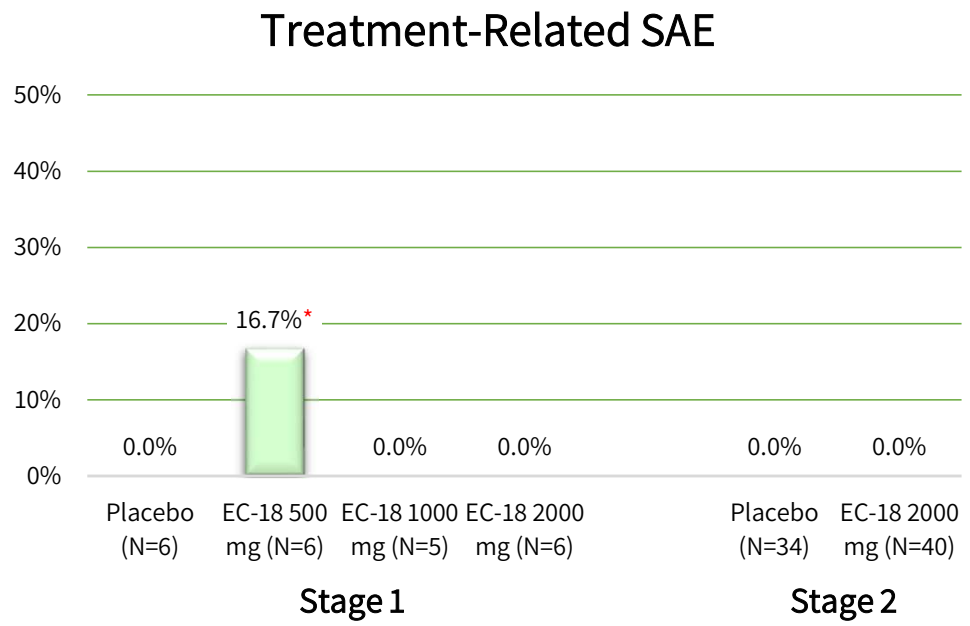
* One unknown HPV Status

Safety Results

Safety Summary

- Comparable safety across all arms
- Attributable to expected chemoradiation-related toxicity





* *Determined to be not related to EC-18*

Treatment-Related AE ≥ 15%

- Comparable across all arms

	Placebo (N=40)		EC-18						Total (N=97)
			500 mg (N=6)		1000 mg (N=5)		2000 mg (N=46)		
	No.	%	No.	%	No.	%	No.	%	%
Any Adverse Events	261.0	92.5	40.0	100.0	37.0	100.0	281.0	95.7	94.8
Nausea	40.0	70.0	5.0	66.7	3.0	40.0	41.0	69.6	68.0
Fatigue	21.0	42.5	4.0	50.0	0.0	0.0	22.0	43.5	41.2
Dry mouth	13.0	32.5	3.0	50.0	3.0	20.0	23.0	43.5	38.1
Dysgeusia	14.0	35.0	3.0	33.3	4.0	40.0	22.0	39.1	37.1
Dysphagia	17.0	40.0	2.0	33.3	1.0	20.0	18.0	34.8	36.1
Stomatitis	15.0	19.6	4.0	50.0	4.0	40.0	18.0	30.4	28.9
Vomiting	17.0	28.3	2.0	33.3	0.0	0.0	19.0	26.1	27.8
Constipation	14.0	30.0	3.0	50.0	0.0	0.0	10.0	21.7	25.8
Weight decreased	15.0	23.9	2.0	33.3	5.0	60.0	14.0	19.6	25.8
Oral pain	9.0	20.0	3.0	50.0	3.0	60.0	9.0	19.6	23.7
Oropharyngeal pain	11.0	22.5	4.0	66.7	0.0	0.0	9.0	17.4	21.6
Radiation skin injury	11.0	21.7	0.0	0.0	1.0	20.0	14.0	21.7	21.6
Diarrhoea	10.0	22.5	2.0	33.3	0.0	0.0	6.0	13.0	17.5
Dehydration	11.0	22.5	1.0	16.7	5.0	40.0	5.0	6.5	15.5

JS1

Conclusions KK0

- Mitigation of the development and the time course of SOM
  - Duration of SOM
  - Incidence of SOM
  - Time to Onset of SOM
  - Time to Opioid Use
- Excellent safety profile comparable to placebo
- Substantial benefits to HPV+ HNC patients treated with low dose cisplatin
- Future analyses include
  - 1-year long-term tumor assessment
  - Biomarker and genomics analyses

Slide 18

KK0 Q: Is there a potential that EC-18 may work in radiation or chemotherapy alone?
Koeun Kim, 2022-05-26T15:15:11.190

SO0 0 Yes, we have seen similar results from our non-clinical CIOM (Chemotherapy-induced Oral Mucositis) and ARS (Acute Radiation Syndrome) indications.
Sookyung Oh, 2022-05-31T19:44:04.514

JS1 What is your plan for Phase 3?
Ji Sun, 2022-05-26T21:28:39.128

SO1 0 We are currently strategizing what our best p3 design options are.
Sookyung Oh, 2022-05-31T19:46:41.243

Acknowledgment

Deep appreciation goes to all our patients and their families, investigators, and site staff