Clinical Pharmacology Review

NDA/eCTD #: 205,489/0027	**EDR Link:** \\CDSESUB1\evsprod\NDA205489\0027
Relevant IND: 109, 108	**Indication:** Attention Deficit Hyperactive Disorder (ADHD)
Formulation: Extended-Release Orally Disintegrating Tablet	**Generic Name:** Methylphenidate
Brand Name: Cotempla XR-ODT	**Strength (mg):** 8.6, 17.3, and 25.9
Submission Type: 505(b)(2) Resubmission	**Submission Date:** December 19, 2016
Sponsor: Neos Therapeutics	**OCP Review Team:** Huixia Zhang; Hao Zhu

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1. EXECUTIVE SUMMARY

Neos Therapeutics is seeking approval of methylphenidate (MPH) in the form of an extended-release orally disintegrating tablet (XR-ODT), for the treatment of Attention Deficit Hyperactive Disorder (ADHD) in patients 6 years old (b) (4), via 505b (2) approach. The listed drug (LD), Metadate CD (NDA21259), is an extended release capsule formulation of MPH, approved in 2001 for the indication of ADHD.

This submission is in response to a complete response (CR) letter issued on November 6, 2015, where several deficiencies in the original submission were identified, the major ones being that adequate linkages among the three formulations developed in the program (i.e., clinical pharmacology formulation, clinical trial formulation, and to-be-marketed formulation [also called commercial scale formulation]), and to the listed drug (LD), Metadate CD, were not established. In the current submission, the Sponsor submitted a relative bioavailability (BA) study to establish the linkages as the Agency recommended in the CR letter.

It was shown in the current and the previous submissions that the efficacy of MPH XR-ODT was demonstrated in children with ADHD (aged 6-12 years old) between 17.3-to-51.8 mg daily dose levels in a classroom study (NT0102.1004) using the clinical trial formulation. Three PK studies: 1) a relative BA study comparing the clinical pharmacology formulation to the LD, Metadate CD (NT0102.1001); 2) a pediatric PK study (NT0102.1003) using the clinical pharmacology formulation; and 3) a relative BA study comparing the clinical trial formulation to the commercial scale formulation of MPH XR-ODT (NT0102.1005), were conducted. Food effect on the commercial scale formulation was also assessed.

OCP's major findings are summarized as follows:

1. Adequate linkages have been established among the three developed formulations (clinical trial formulation, clinical pharmacology formulation, and commercial scale [to-be-marketed] formulation), and to the Listed Drug, Metadate CD, through two relative BA studies, in combination with the knowledge that the quantities of release-controlling (b) (4) used in the clinical pharmacology formulation are bracketed by the clinical trial formulation and the to-be-marked formulation.
2. MPH XR-ODT is efficacious in the treatment of ADHD in children aged 6-12 years old.
3. Similar shapes of PK profiles are demonstrated in children (6-12 years old), adolescents, and adults. Therefore, the pharmacodynamic profiles are anticipated to be similar in the three patient populations.
4. Though exposure to MPH is less in adolescents and adults compared to children after the same dose administration of MPH XR-ODT, optimal clinical response can be achieved by titration.
5. MPH XR-ODT is not bioequivalent to Metadate CD, the LD. However, the efficacy and safety profiles are established in a clinical trial in patients 6-12 years of age.
6. MPH XR-ODT can be administered with or without food. However, patients are advised to take MPH XR-ODT either with food or with an empty stomach consistently to ensure consistent clinical response.
7. Patients should avoid concomitant use with gastric pH modulators (e.g., a proton pump inhibitor or a H_2-blocker), because altered pharmacodynamic profile due to increased drug release from MPH XR-ODT at elevated gastric pH is anticipated.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval for MPH XR-ODT. Per the recommendation (Appendix) from the Office of Study Integrity and Surveillance (OSIS), the data from the pivotal relative bioavailability study is considered acceptable. No inspection of the clinical or analytical site for the pivotal study 1005 was deemed necessary, because those sites were recently inspected and no issues were identified. The acceptability of specific drug information is provided below.

Decision	**Acceptable to OCP?**	**Comment**
Overall	☒ Yes ☐ No	Pending labeling agreements with the sponsor
Evidence of effectiveness	☒ Yes ☐ No	One positive registration trial in patients 6-12 years old.
BE (MPH XR-ODT *vs* Metadate CD)	☐ Yes ☒ No	Approval will be based on efficacy trial, not BE result.
Proposed dose for general patients	☒ Yes ☐ No	Same as for the LD
Labeling	☐ Yes ☒ No	Pending satisfactory agreement with the sponsor

1.2 Phase IV Commitments

Office of Clinical Pharmacology proposes the following post-marketing study.

PMC or PMR	**Key Drug Development Question**	**Rationale**	**Design Summary (TBD)**
☐ PMC ☒ PMR	What are the PK properties of MPH XR-ODT in children (4 to 5 years of age) with ADHD?	Concentration time profile of MPH determines the onset and duration of the clinical response (i.e., efficacy and safety). It is valuable to assess the PK profiles in patients 4-5 years old with ADHD and ensure its similarity to that in older patients. In addition, this information can help inform dose selection and safety monitoring for the clinical efficacy and safety trial.	Study population: patients 4-5 years old with ADHD Study design: single dose, open label Sample size: prospectively powered to ensure a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution Dose: relevant dose expected to be used in the patient age group Endpoints: AUC, C_{max} Final Protocol Submission: January 2018 Study/Trial Completion: February 2020 Final Report Submission: August 2020

2. QUESTION BASED REVIEW

2.1 What are the compositional differences in the formulations developed for MPH XR-ODT? Is adequate linkage established among them and to the listed drug Metadate CD?

Three formulations were developed in the program: a clinical pharmacology formulation (Lot: 1E101A), a clinical trial formulation (Lot: 2E116E), and a commercial-scale (to-be-marketed) formulation; and they were used in different trials of the program (Table 1).

Table 1: Formulations used in the development program

Submission	Study	Formulation used	Lot #
Original	Relative BA	Clinical pharmacology formulation *vs* Metadate CD	1E101A
	Food effect	Clinical pharmacology formulation	1E101A
	Pediatric PK	Clinical pharmacology formulation	1E101A
	Clinical efficacy	Clinical trial formulation	2E116E3
2nd round	Relative BA/BE; food effect	Clinical trial formulation *vs* commercial scale formulation	2E116E3 *vs* 6P081E

There are compositional differences in the aforementioned formulations, and the major difference resides in the release control components (Table 2). The commercial scale formulation will have about (b) (4)% (w/w) (b) (4) extended release and (b) (4)% (w/w) (b) (4) delayed release (b) (4) than the clinical trial formulation used in the efficacy trial. In addition, there is about (b) (4)% change on the release controlling (b) (4) between the clinical pharmacology formulation and the clinical trial formulation. However, it is noted that the amount of the release controlling (b) (4) of the clinical pharmacology formulation is bracketed by that of the clinical trial formulation and the commercial scale formulation (Table 2).

Table 2: Composition difference in the release control components of the MPH XR-ODT formulations

(b) (4)		Function	Clinical trial formulation	Clinical pharmacology formulation	Commercial scale formulation
Extended Release/ Delayed Release (ER/DR) (b) (4)	Lot#	--	2E116E	1E101A	6P081
	(b) (4)				

To bridge the findings from the LD, Metadate CD, to the commercial scale formulation, and to extend the findings from the efficacy and safety trial using the clinical trial formulation to the commercial scale formulation, two relative BA studies, including 1) a relative BA trial comparing the clinical pharmacology formulation to the LD, Metadate CD; and 2) a relative BA trial comparing the clinical trial formulation to the commercial scale formulation, were conducted to establish the linkages.

1) A relative BA trial comparing the clinical pharmacology formulation to the LD, Metadate CD

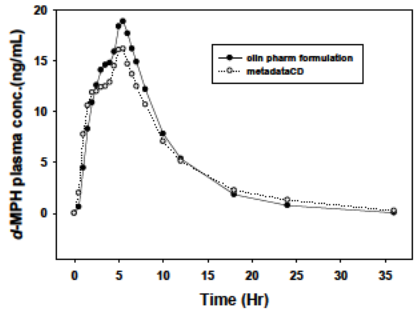
After same dose administration (51.8 mg MPH XR-ODT has the same amount of MPH base in 60 mg Metadate CD), compared to the LD, the mean C_{max} of total MPH following MPH XR-ODT (clinical pharmacology formulation, lot 1E101A) in healthy adults was approximately 25% higher with the 90% CI of the C_{max} ratio out of the 80-125% limits, while mean AUC_{inf} was similar with the 90% CI of the AUC_{inf} ratio within 80-125% range (Table 3). Additionally, the reported partial AUC analysis didn't meet the Guidance recommendation. Even though the two formulations are not considered bioequivalent, the results suggested that an adequate linkage has been established between the clinical pharmacology formulation and the LD.

Table 3: PK Parameters (Mean ±SD) of (*d*+*l*)-MPH Following Administration of 51.8 mg MPH XR-ODT (Clinical Pharmacology Formulation) or Metadate CD under Fasting Conditions

Parameters	Test (T, n=38)	Reference (R, n=38)	Geomean Ratio (T/R, 90% CI)
C_{max} (ng/mL)	21.2±5.5	17.4 ±5.8	126.0 (119.4, 133.0)
T_{max} (hr)	5.0±1.0	5.0±1.1	--
AUC_{0-3} (hr*ng/mL)	22.7±8.1	25.7±9.2	93.5 (85.7, 102.1)
AUC_{0-tmax}(hr*ng/mL)	54.0±17.1	53.1±17.1	104.8 (97.9, 112.2)
$AUC_{tmax-24}$(hr*ng/mL)	112.5±44.4	104.3±44.7	111.7 (106.7, 116.9)
$AUC_{tmax-last}$(hr*ng/mL)	114±48.3	111.4±49.9	105.9 (100.7, 111.4)
AUC_{last} (hr*ng/mL)	168±57.4	164.5±65.1	106.8 (103.2, 110.6)
AUC_{inf} (hr*ng/mL)	171.8±58.0	170±66.2	105.5 (102.2, 109.0)
$T_{1/2}$ (hr)	4.0±0.7	6.0±1.6	--

Test: clinical pharmacology formulation , 51.8 mg; Reference: listed product-Metadate CD, 60 mg
-Source: Table 11.4.3.6 of CSR

Figure 1: Mean Concentration Time Profile of *d*-MPH Following Administration of MPH XR-ODT (51.8 mg, Clinical Pharmacology Formulation) or Metadate CD (60 mg) under Fasting Conditions



2) A relative BA trial comparing the clinical trial formulation to the commercial scale formulation

The clinical trial formulation and the commercial scale formulation of MPH XR-ODT are considered bioequivalent based on both conventional BE variables (i.e., C_{max} and AUC_{inf}) and

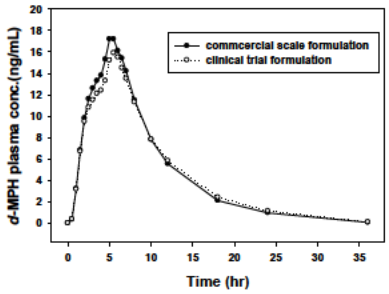
partial AUC metrics (i.e., AUC_{0-3}, AUC_{3-7}, AUC_{7-12}) recommended by the MPH BE guidance. In addition, the shapes of the average pharmacokinetic profiles between the two formulations are similar.

Table 4: PK Parameters (Mean ± SD) of *d+ l* MPH Following Administration of 51.8 mg MPH XR-ODT in Healthy Adults under Fasted Conditions

Parameters	Clinical Trial Formulation (T, n=47)	Commercial Scale Formulation (R, n=48)	Geomean Ratio (T/R, 90% CI)
C_{max} (ng/mL)	17.5 ±5.5	19.5 ±6.5	91.6 (85.2, 98.5)
T_{max} (hr)[#]	5.5 (3.0, 7.0)	5.0 (2.0, 7.0)	--
AUC_{0-3} (hr*ng/mL)	19.0±6.7	19.9±8.8	101.1 (85.3, 119.9)
AUC_{3-7}(hr*ng/mL)	57.1±17.6	62.3±20.2	93.7 (86.9, 101.0)
AUC_{7-12}(hr*ng/mL)	46.1±22.3	46.2±22.8	101.4 (93.8, 109.6)
AUC_{inf} (hr*ng/mL)	166.5±71.6	167.7±68.6	100.5 (94.7, 106.6)
$T_{1/2}$ (hr)	4.5±0.8	4.4±0.6	--

[#]T_{max} presented as median (min, max); *-Source: Table 11.4.3.4 of CSR*

Figure 2: Mean Concentration Time Profile of *d*-MPH Following Administration of 51.8mg MPH XR-ODT in Healthy Adults under Fasted Conditions



To summarize, because the commercial scale formulation is found BE to the clinical trial formulation, the efficacy and safety findings based on the clinical trial formulation can be extended to the commercial scale formulation.

In addition, an adequate bridging has been established between the commercial scale formulation and the LD, metadata CD through two relative BA trials in combination with the knowledge that the quantities of release-controlling (b) (4) used in the clinical pharmacology formulation are bracketed by the clinical trial formulation and the commercial scale formulation. In the first relative BA trial, the clinical pharmacology formulation is linked to the LD. In the second relative BA trial, the clinical trial formulation is linked to commercial scale formulation. The quantities of the release-controlling (b) (4) used in the clinical pharmacology formulation are bracketed by the clinical trial formulation and the commercial scale formulation. Hence, once the bridging between the clinical trial formulation and the commercial scale formulation is established, an adequate bridging between the commercial scale formulation and the LD is expected.

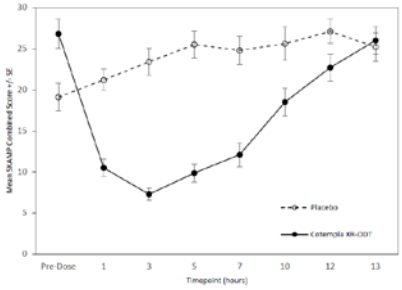
2.2 Is there evidence of effectiveness for MPH XR-ODT in children aged 6-12 years old?

Yes. The efficacy of MPH XR-ODT in children (6 to 12 years of age) with ADHD was demonstrated in trial NT0102.1004 using the clinical trial formulation.

Study NT0102.1004 was a randomized, multicenter, double-blind, placebo-controlled, parallel group, laboratory classroom study. In the open-label dose optimization phase (4 weeks), the initial dose for all subjects was 17.3 mg once daily in the morning. The dose could be titrated on a weekly basis from 17.3 mg, to 25.9 mg, to 34.6 mg, and up to 51.8 mg until an optimal dose or the maximum dose of 51.8 mg/day was reached. At the end of this period, subjects remained on their optimized dose for an additional week. Subjects then entered a 1-week randomized, double-blind, parallel group treatment period with the individually optimized dose of COTEMPLA XR-ODT or placebo.

The primary efficacy endpoint was the average of the SKAMP-Combined (Attention and Deportment) scores over the test day (not including the baseline score), with assessments conducted at baseline, and 1, 3, 5, 7, 10, 12, and 13 hours post-dosing, and this endpoint was met (Figure 3).

Figure 3: LS Mean SKAMP Combined Score after Treatment with COTEMPLA XR-ODT or Placebo during Classroom Day



2.3 Can the efficacy findings be extended from pediatric patients aged 6-12 years old to adolescents and adults for MPH XR-ODT?

The age range to which the efficacy findings from pediatric patients aged 6-12 years old can be extended for MPH XR-ODT is dependent on the approved population for the LD, Metadate CD. From a clinical pharmacology's perspective, similar pharmacodynamic profiles in adolescents and adults can be expected based on the following findings:

a. MPH is shown to be efficacious in several clinical trials across a varied range of formulations in patients 6 years and older.
b. MPH XR-ODT (17.3mg to 51.8mg) was shown to be effective in the treatment of ADHD in children (6-12 years).
c. The shapes of PK profiles of MPH XR-ODT in children, adolescents, and adults are similar (See Question 2.4).
d. Though exposure to MPH is less in adolescents and adults compared to children after the same dose administration of MPH XR-ODT, optimal clinical response can be achieved by titration. It is expected that MPH XR-ODT is effective in adolescent and adult patients.

2.4 What are the PK properties of d-MPH after single dose administration of MPH XR-ODT in children 6-12 years of age, adolescents, and healthy adults?

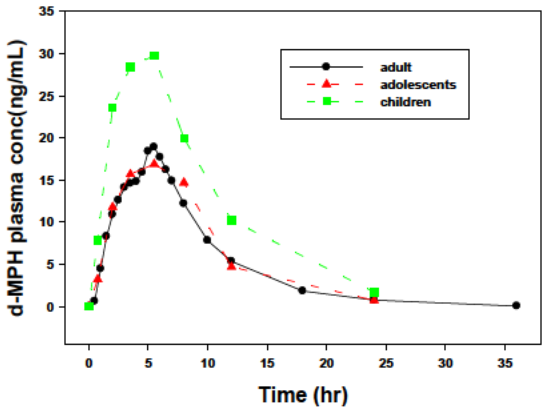
MPH XR-ODT is an extended release orally disintegrating tablet that contains about (b)(4)% IR and (b)(4)% ER of MPH HCl. Following a single dose administration of 51.8 mg MPH XR-ODT to healthy volunteers under fasted conditions, MPH reached C_{max} in about 5.0 hours post dose (Table 5, Figure 4), with an estimated half life of about 4 hours. Similar PK profiles (Figure 4) and parameters for T_{max} and $T_{1/2}$ were obtained in children 6-12 years and adolescents with ADHD, and healthy adults (Table 5). Body-weight corrected clearance values were also similar across the three populations.

Table 5: PK Parameters (Mean ± SD) of *d*-MPH After MPH XR-ODT (2x25.9mg) Administration Under Fasted Conditions (Clinical Pharmacology Formulation)

PK Parameters	Children (6-12 yrs, n=24)	Adolescents (13-17 yrs, n=8)	Adults (n=38)
T_{max} (hr)#	4.5(2.0,8.0)	5.5 (3.5, 8.0)	5.0 (2.5, 6.5)
C_{max} (ng/mL)	32.7±9.8	20.2±5.8	20.8±5.2
AUC_{inf} (hr*ng/mL)	329±90.2^	187±62.1*	169±57.1
$T_{1/2}$ (hr)	4.4±1.0^	3.9±0.3*	4.0±0.7
Cl/F/weight (L/hr/kg)	6.2±1.5^	5.5±1.2*	5.5±1.2

#T_{max} presented as median (min, max); * n=7 ^n=23

Figure 4: Mean Concentration Time Profile of *d*-MPH Following Administration of 51.8 mg MPH XR-ODT (Clinical Pharmacology Formulation) under Fasted Conditions



With an estimated half life (~4 hr) and once daily dosing regimen, the pharmacokinetic parameters of MPH XR-ODT is not expected to change after multiple dosing compared to single dose administration (MPH demonstrates time-independent linear pharmacokinetics). The first dose is almost completely eliminated from the body at the end of 24 hour period, and no significant accumulation of methylphenidate is expected.

2.5 Does food affect the absorption/pharmacokinetics of MPH following the administration of MPH XR-ODT?

High-fat, high-calorie meal decreased mean C_{max} of total MPH about 24%, and increased mean AUC_{inf} about 16% in subjects taking 51.8 mg MPH XR-ODT (commercial scale formulation).

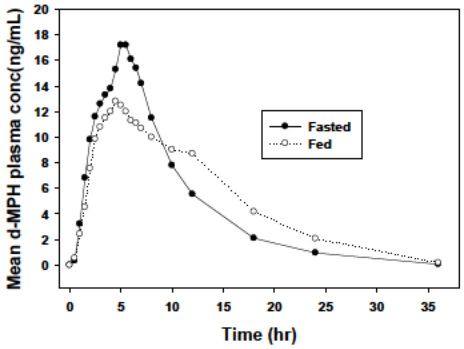
Food shortened median T_{max} from 5.0hr (fasted state) to 4.5hr (fed state) and altered the underlying pharmacokinetic profiles. Because MPH products demonstrate strong correlation between MPH concentration and clinical response, to minimize variation on clinical response, patients should take MPH XR-ODT consistently either with food or with an empty stomach.

Table 6: PK Parameters (Mean ± SD) of *d*- MPH After Administration of 51.8 mg MPH XR-ODT (Commercial Formulation) Under Fasting or Fed Conditions

Parameters	Fed (n=47)	Fasted (n=48)	Geomean Ratio (Fed/Fasted, 90% CI)
C_{max} (ng/mL)	14.5±4.2	19.5 ±6.5	76.1 (70.8, 81.9)
T_{max} (hr)	4.5 (2.0, 12.1)	5.0 (2.0, 7.0)	---
AUC_{inf} (hr*ng/mL)	189±67.3	167.7±68.6	115.9 (109.1, 123.1)
$T_{1/2}$ (hr)	4.8±0.9	4.4±0.6	---

-Source: Table 11.4.3.5 of CSR

Figure 5: Mean Concentration Time Profile of *d*-MPH Following Administration of 51.8 mg MPH XR-ODT under Fasted or Fed Conditions



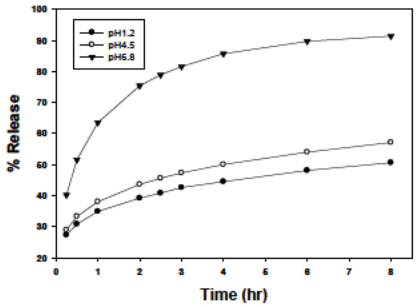
2.6 Is there a potential for drug-drug interaction between MPH XR-ODT and a gastric pH modulator (e.g., a proton pump inhibitor or a H_2-blocker)?

MPH XR-ODT showed pH-dependent dissolution solubility (Figure 6). At hour 0.5, which is close to the estimated mean gastric empty time (38min) when the stomach was empty (Ewe K et al., 1991: Dig Dis Sci 1991: 36: 146-52), percentage released of MPH from the ODT tablet was increased about 67% when media pH was increased from 1.2 to 6.8. At hour 2.5, which is the estimated mean gastric empty time post a standard meal (Hellmig S. et al., 2006: J Gastroenterol Hepatol 21:1832-8), percentage released of MPH from the ODT tablet was increased about 93% when media pH was increased from 1.2 to 6.8.

The increased release of MPH from the MPH XR-ODT at an elevated gastric pH could potentially lead to increased drug absorption and subsequently change the concentration time profile of MPH *in vivo*. It is well accepted that for MPH products, the shape of the PK profile is highly correlated with its pharmacological effect. It is anticipated that coadministration of a gastric pH modulator (e.g., a proton pump inhibitor or a H_2-blocker) may yield altered

pharmacodynamic profiles. Hence, it is recommended that patients should avoid concomitant use with gastric pH modulators (e.g., a proton pump inhibitor or a H_2-blocker).

Figure 6: Mean Dissolution Profiles of MPH in Aqueous Solution with Different pH (MPH XR-ODT, 25.9mg, Clinical Trial Formulation)



-source: Appendix Table MD 13, 16, 19 in disso-method-devl-report.pdf

3. OFFICE OF STUDY INTEGRITY AND SURVEILLANCE MEMO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/13/2017

TO: Division of Psychiatry Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 205489

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Clinical	Worldwide Clinical Trials Early Phase Services, LLC.	2455 NE Loop 410, Suite 150, San Antonio, TX

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/s/

SHILA S NKAH
02/17/2017

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HUIXIA ZHANG
06/14/2017

HAO ZHU
06/14/2017

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