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*APPLICATION NUMBER:*  
**202020Orig1s000**

**SUMMARY REVIEW**

## SUMMARY REVIEW OF REGULATORY ACTION

Date: July 25, 2012

From: Badrul A. Chowdhury, MD, PhD  
Director, Division of Pulmonary, Allergy, and Rheumatology,  
Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 20-2020

Applicant Name: Horizon Pharma USA, Inc.

Date of Submission: September 26, 2011

PDUFA Goal Date: July 26, 2012

Proprietary Name: Rayos

Established Name: Prednisone

Dosage form: Tablet, delayed-release

Strength: 1 mg, 2 mg, and 5 mg

Proposed Indications: Treatment of rheumatoid arthritis in adult patients

Action: Approval

### 1. Introduction

Horizon Pharma submitted this 505(b)(2) new drug application for use of Rayos (prednisone) delayed-release tablets for the treatment of rheumatoid arthritis in adult patients. The proposed starting dose is 5 mg administered once per day at bedtime with the recommendation that the dosage be individualized according to the severity of the disease and response to treatment. This application references immediate-release prednisone (NDA 17109 Roxane Labs), which was approved for a broad range of indications, including the treatment of rheumatoid arthritis. NDA was withdrawn, effective May 29, 2002. This summary review will provide an overview of the application, with a focus on the regulatory history and the development program.

### 2. Background

Prednisone was first used to successfully treat rheumatoid arthritis in the late 1940s and is now used to treat a wide range of diseases associated with an inflammatory component. Oral, immediate-release prednisone is widely available as a generic drug and is approved for multiple inflammatory arthritides and other inflammatory, non-rheumatologic conditions. Prednisone tablets are indicated as adjunctive therapy for short-term administration or low dose maintenance therapy of rheumatoid arthritis including juvenile rheumatoid arthritis (juvenile inflammatory arthritis), and various other diseases.

The rationale for development of Rayos delayed-release tablets specifically for rheumatoid arthritis is the delayed-release characteristics of the product compared to immediate-release prednisone tablets (described further below in Sections 2 and 4). Immediate-release oral prednisone is typically administered in the morning to coincide with the circadian pattern of adrenal cortex activity in order to minimize the suppression

of adrenocorticoid activity, as noted in the current prednisone label. Certain rheumatoid arthritis symptoms such as joint pain and stiffness also exhibit a circadian pattern, presumably secondary to elevated levels of pro-inflammatory cytokines in the early morning. Horizon Pharma contends that typical morning administration of immediate-release prednisone is not synchronized with this early-morning cytokine rise that occurs prior to patient awakening. To address this diurnal variability in cytokine release, Horizon developed Rayos delayed-release prednisone formulation to be taken once daily at bedtime, designed to release prednisone in the early-morning hours without compromising patient convenience. Horizon Pharma postulates that the earlier administration of daily prednisone will result in more efficacious treatment of rheumatoid arthritis symptoms, particularly the symptom of early morning stiffness.

Horizon Pharma and the Agency had various regulatory interactions that included a pre-IND meeting with the then Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) on March 24, 2006, an End-of-Phase 2 meeting with DAARP on December 13, 2007, and a pre-NDA meeting with DAARP on January 26, 2010.

At the pre-IND meeting, Horizon Pharma proposed a development program [REDACTED] (b) (4)

[REDACTED] At that time Horizon Pharma had manufactured the delayed-release prednisone product (now commercially called Rayos), and the CMC characteristics of the product were defined. Horizon Pharma described its ongoing European development program, comprised of bioavailability trials comparing their delayed-release prednisone product to an EU-approved prednisone immediate-release formulation (Decortin) and a clinical trial comparing the delayed-release prednisone product to an immediate-release prednisone product with morning stiffness as a novel primary endpoint. DAARP [REDACTED] (b) (4)

[REDACTED] suggested a general rheumatoid arthritis treatment indication based on a standard endpoint such as the ACR20 (American College of Rheumatology response criteria for 20% improvement) with morning stiffness as a secondary outcome, adding that the acceptability of morning stiffness as a secondary claim would be a review issue. At the End-of-Phase 2 meeting, Horizon Pharma stated that the clinical trial comparing the delayed-release prednisone product to an immediate-release prednisone product with morning stiffness as a novel primary endpoint was complete. In response to DAARP's advice at the Pre-IND meeting in 2006, Horizon Pharma proposed to conduct an additional Phase 3 trial, a placebo-controlled trial with ACR20 response rate as the primary endpoint and patient-reported morning stiffness as a key secondary endpoint. DAARP at that time stated that the proposed program appeared reasonable to support a general rheumatoid arthritis treatment indication but noted that the acceptability of morning stiffness as a secondary claim in the label would be a review issue. At the pre-NDA meeting, DAARP confirmed that positive ACR20 results from the placebo-controlled Phase 3 trial would support a general rheumatoid arthritis treatment indication given the established efficacy and safety profile of immediate-release prednisone for rheumatoid arthritis. DAARP stated that the morning stiffness data might be included in the Clinical Studies section of the label pending review.

Although DAARP at the various regulatory meetings with Horizon Pharma in principle accepted a development program based on clinical studies to support a general rheumatoid arthritis indication with a potential claim for morning stiffness, there are some points worth noting. First, prednisone is known to be effective in rheumatoid arthritis and immediate-release prednisone already has a rheumatoid arthritis indication. Therefore, a clinical trial to show general efficacy of a delayed-release formulation of prednisone for rheumatoid arthritis is not necessary to support approval. An appropriate study design to tease out a morning stiffness benefit claim would require comparison of the delayed-release formulation to an immediate-release formulation. Second, any anti-inflammatory treatment that positively impacts rheumatoid arthritis would be expected to improve morning stiffness along with other signs and symptoms, and this effect may not be unique to a delayed-release prednisone formulation. Third, there is no reason to believe that the delayed-release prednisone would not be effective in various other diseases where immediate-release prednisone is known to be effective. At the time of earlier meetings between Horizon Pharma and DAARP, a potential path for marketing approval of the delayed-release prednisone (now called Rayos) based only on CMC and clinical pharmacology data was not discussed.

### **3. Chemistry, Manufacturing, and Controls**

The proposed commercial drug product, Rayos, consists of an immediate-release prednisone core tablet that is surrounded by an inactive outer tablet shell that gives it the delayed-release characteristics. Drug release is triggered by penetration of water into the outer tablet shell, (b) (4)

(b) (4) After a delay time of approximately (b) (4) hours in in vitro dissolution testing, the outer tablet shell opens into two halves and the core tablet then releases the prednisone active drug substance in a manner that is similar to an immediate-release tablet. The total tablet weight of Rayos is 410 mg, (b) (4)

(b) (4) All excipients used in the drug product are compendial. The drug product will be of three strengths of prednisone, 1 mg, 2 mg, and 5 mg, each packaged in bottles of 30 tablets and 100 tablets. The prednisone drug substance is manufactured by Tianjin Tianyao, Tianjin, China. The drug product is manufactured by Bayer Pharma AG, Germany, and by Aenova France SAS, France. All manufacturing and testing facilities associated with this application have an acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate. An expiry of 30 months is proposed and supported by submitted data.

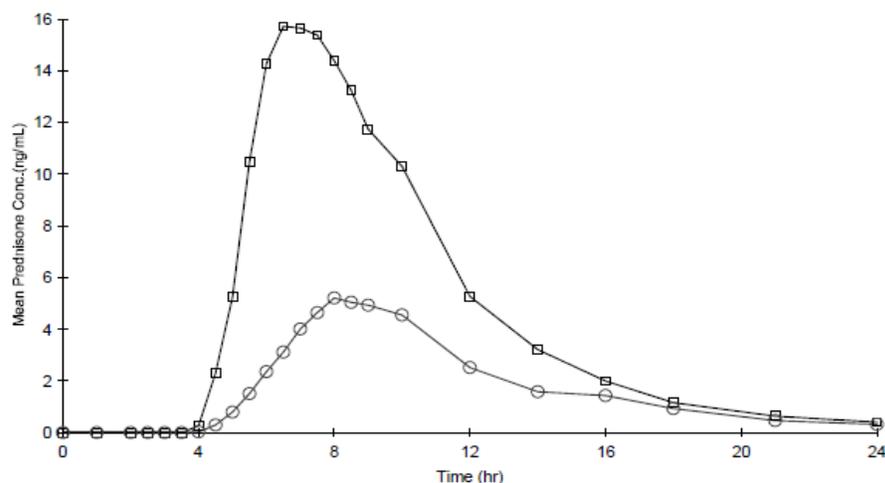
### **4. Nonclinical Pharmacology and Toxicology**

No new nonclinical studies were submitted or required. This application relies on the previously approved immediate release prednisone tablet.

### **5. Clinical Pharmacology and Biopharmaceutics**

The pharmacokinetic properties of immediate-release prednisone are well known and generally apply to Rayos. Immediate-release prednisone is well absorbed following oral

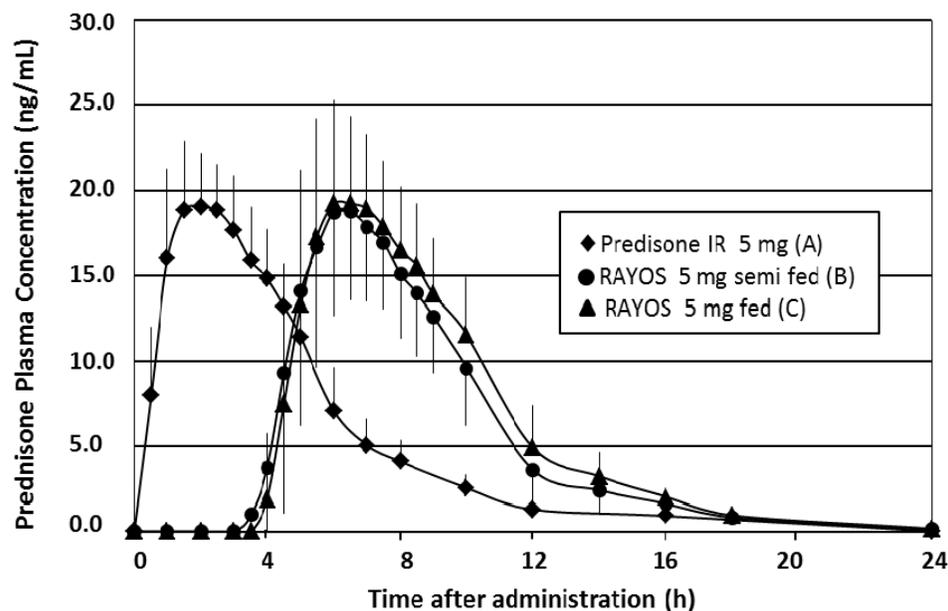
administration with an absolute systemic bioavailability averaging 80-100% and a  $T_{max}$  of 1 to 2 h. Administration with food does not affect the extent of absorption. Prednisone is almost completely metabolized to its active metabolite prednisolone. Systemic levels of prednisolone are 4- to 10-fold higher than those of prednisone. The elimination half-lives for both prednisone and prednisolone are 2-3 hours. There are two characteristics that are unique for Rayos. First, Rayos has a pronounced food effect that is not present for immediate-release prednisone. Second, Rayos has a delayed  $T_{max}$  compared to immediate-release prednisone.



**Figure 1.** Effect of food on pharmacokinetics of Rayos Tablets (□ – fed state; ○ – fasted state)

Figure 1 shows results of food effect study conducted with Rayos Tablets. Both the  $C_{max}$  and AUC for both prednisone and prednisolone under fed conditions are about three times those under fasted conditions.

Figure 2 shows results of a bioavailability study comparing the delayed-release Rayos Tablets and immediate-release Decotrin Tablets. Because of a significant food effect of the delayed-release formulation, the relative bioavailability study was conducted with the delayed-release Rayos Tablets given under semi-fasted or fed condition and the immediate-release reference tablets given under fasted condition. The exposures of both prednisone and prednisolone from Rayos were comparable to those from immediate-release tablets under fasted condition. However, the  $T_{max}$  was delayed 4 hours for Rayos as compared to immediate-release tablets (Figure 2). The exposure of prednisone and prednisolone from immediate release tablets was not affected by the intake of food (data not shown in this review).



**Figure 2. Mean plasma levels of prednisone after a single dose of 5 mg prednisone administered as a 5 mg Rayos (prednisone) delayed-release tablet or a 5 mg prednisone immediate release tablet. [A: 5 mg IR tablet under fasting conditions, administered at 2 am, B: 5 mg RAYOS, administered 2.5 hours after a light evening meal, and C: 5 mg RAYOS administered immediately after dinner.]**

The clinical pharmacology data show that other than the food effect and the four-hour delayed exposure, Rayos is similar to immediate-release prednisone tablets. The food effect and the four-hour delayed release makes Rayos a different product than immediate-release prednisone tablets, but these characteristics do not provide any unique efficacy advantages or unacceptable safety concerns. The four-hour delayed release characteristic of Rayos by itself is of no clinical significance because the eventual PK profile is similar to that of immediate-release prednisone tablets. Decreased exposure without food does not raise unacceptable safety concerns for Rayos because prednisone is used in clinical practice at a wide range of doses and dose-related safety issues with prednisone are well understood. Food effect does not raise unacceptable efficacy concerns because dose or prednisone is generally titrated to desired effect. However, because of the food effect, the product label will recommend that Rayos be taken with food.

## 6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

## 7. Clinical and Statistical – Efficacy

### a. Overview of the clinical program

Some characteristics of the clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these

studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

**Table 1. Relevant clinical studies with Rayos in patients with rheumatoid arthritis**

ID Year *	Study Characteristics - Study design - Study duration - Patient age, mean (range)	Treatment groups †	N ‡	Primary efficacy variable §	Regions
003 2004-2006	- Parallel arm, double blind - 12 week - 55 (22 – 79) yr	Rayos 3-10 mg q PM Pred IR 3-10 mg q AM	144 144	Morning stiffness	Germany, Poland
007 2008-2009	- Parallel arm, double blind - 12 week - 57 (27 – 80) yr	Rayos 5 mg q PM Placebo	231 119	ACR 20	US, Canada, W Europe
	- 9 month open label safety	Rayos 3-10 mg q PM	249		

\* Study ID shown abbreviated from Horizon Pharma’s study number. Year shows when study subject enrollment was started and completed.  
† Rayos was dosed at 10 PM; Pred IR (immediate release prednisone) was dosed between 6 and 8 AM.  
‡ Number randomized  
§ ACR20 = Proportion of patients achieving 20% improvement from baseline in American College of Rheumatology defined criteria

b. Design and conduct of the studies

Studies 003 and 007 were randomized, double-blind, active controlled (study 003) or placebo controlled (study 007), and conducted in patients 18 years of age and older with moderate to severe rheumatoid arthritis diagnosed according to accepted criteria. Patients in the trials had received DMARDs for at least 3 months (study 003) or 6 months (study 007). The primary efficacy variables in the two studies are listed in Table 1. These were assessed at week 12. A key secondary efficacy variable in study 007 was morning stiffness. Morning stiffness assessment was based on patient diary queries where patients were asked to record daily the time of wake-up and the time of resolution of morning stiffness. Other efficacy variables included the DAS28, quality of life SF-36, and assessment of fatigue. Safety assessment included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECG.

There are no validated PRO instruments for the assessment of morning stiffness, and Horizon Pharma did not submit any validation data to support the use of the patient diary queries. These data were requested to address the concerns specific to the instrument raised in a consult from the Agency’s Study Endpoints and Label Development team (SEALD). The SEALD consult noted a lack of information to support reliability and construct validity and recommended that Horizon Pharma provide scientific justification for a clinically meaningful change and discussion regarding translation and cultural adaptation of the instrument, as outlined in the 2009 PRO guidance. However, morning stiffness is not a novel claim for rheumatoid arthritis drugs.

c. Efficacy findings and conclusions

The clinical program shows the efficacy of Rayos for the treatment of rheumatoid arthritis.

Results from study 007 show efficacy of Rayos in rheumatoid arthritis. The ACR20 response rates were higher in patients treated with Rayos compared to placebo (47% vs. 29%) and the difference between the treatment groups was 17% (95% CI of [7, 28],  $p=0.001$ ). Various sensitivity analyses conducted with different imputations for missing data (observed case, LOCF, withdrawal) also showed efficacy. The ACR50 response, ACR70 response, components of ACR criteria responses, and ACR20 response over 12 weeks also showed higher response rates in patients treated with Rayos compared to placebo. These positive results are consistent with the known efficacy of prednisone in the treatment of rheumatoid arthritis.

A morning stiffness benefit for Rayos in rheumatoid arthritis was assessed in study 007 as a secondary endpoint (compared to placebo) and as a primary endpoint in study 003 (compared to immediate-release prednisone). Statistically significant differences between Rayos and the comparators were seen in both studies, but there are various issues with study 003 that preclude any comparative claims between Rayos and immediate-release prednisone. There were major protocol deviations in study 003, including study medication taken out of the specified time range and too short duration of morning stiffness. The morning stiffness efficacy result was not robust when evaluated with certain sensitivity analyses; for example, there was no statistically significant difference between treatment groups for this endpoint in the per-protocol population. It is also worth noting that the active comparator, immediate-release prednisone, had virtually no effect on morning stiffness in study 003, which is somewhat surprising when compared to the placebo effect observed in study 007. Furthermore, Horizon Pharma was not able to provide financial disclosure information for study 003, and states that information from study 003 was submitted only in support of safety and not efficacy. Nevertheless, based on the results from study 007, the data are adequate to support a morning stiffness claim for Rayos compared to placebo. In study 007, patients treated with Rayos had a median decrease in the duration of morning stiffness of 55 minutes compared to 33 minutes in placebo treated patients (estimated median difference between treatment groups was 20 minutes with 95% CI of 17, 32).

The mean change in DAS28 at week 12 between Rayos and placebo treatment groups was statistically significantly different, but the proportion of responders (defined as  $\text{DAS28} < 2.6$ ) between the Rayos and placebo treatment groups was not different. Also multiplicity issues were not considered for analysis of DAS28, or many secondary endpoints such as SF36 and fatigue.

## 8. Safety

### a. Safety database

The safety assessment of Rayos is based on studies listed on Table 1 and the known safety profile of immediate-release prednisone.

### b. Safety findings and conclusion

The submitted data support the safety of Rayos for the typical indications approved for immediate-release prednisone. Adverse events seen in the Rayos clinical program were typical of findings expected in an older population with long standing rheumatoid arthritis with other comorbid conditions and administration of prednisone. The Rayos clinical program did not raise safety concerns beyond those already known for immediate-release prednisone.

### c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

## 9. Advisory Committee Meeting

An Advisory Committee meeting was not convened for this application because prednisone is a well-known drug and the efficacy and safety of prednisone in rheumatoid arthritis and various other diseases are well accepted. However, a Regulatory Briefing was held on May 18, 2012, to discuss possible regulatory pathways for approval and labeling. The discussants agreed that the CMC and clinical pharmacology data are sufficient for approval of Rayos for a general rheumatoid arthritis indication and also various other indications approved for immediate-release prednisone. The main regulatory question was how to handle the results of a clinical program that were requested previously by DAARP but are not necessary for approval (detailed in sections 2, 5, and 7 above). The merit of including the placebo-controlled clinical study in the label was considered debatable. Morning stiffness could be a supportable claim for the product label, but the submitted data are not adequate for comparative claims between Rayos and immediate-release prednisone.

A follow-up meeting to the Regulatory Briefing was held with the Director of Office of New Drugs, the Deputy Center Director for Clinical Sciences, and this Division on July 3, 2012, to further discuss regulatory pathways for approval and labeling. The consensus was that the CMC and clinical data are adequate for approval and that the addition of new efficacy or safety data are not required to support approval of the application. A label that maintained consistency with the approved labeling for immediate-release prednisone is most appropriate, including labeling for the broad range of indications. (b) (5)

. Inclusion of clinical study data in the label limited to the primary endpoint and supported secondary endpoints from study 007 would be reasonable, with balancing disclaimer language that stated that a benefit for Rayos compared to immediate-release prednisone had not been established.

## 10. Pediatric

As a new dosage form, Rayos triggers pediatric studies as required under the Pediatric Research Equity Act. [REDACTED] (b) (4)

However, based on the information in the NDA, the review team concluded that the pediatric requirements were already fulfilled and recommended that Rayos be labeled for all the indications and full age range approved for the reference product, immediate-release prednisone. This proposal was discussed with the Pediatric Research Committee on June 27, 2012, who concurred with the Division's assessment.

## 11. Other Relevant Regulatory Issues

### a. DSI Audits

DSI audits were not requested for the clinical program because prednisone is a well-characterized corticosteroid with a known efficacy and safety profile. During review of the submission, no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

### b. Financial Disclosure

Horizon Pharma submitted acceptable financial disclosure statements for study 007. As noted previously in Section 7c, Horizon Pharma was not able to provide financial disclosure information for study 003 and states that information from study 003 is submitted only in support of safety and not efficacy.

### c. Other

There are no outstanding issues with consults received from OPDP (formerly known as DDMAC), DMEPA, or from other groups in CDER.

[REDACTED] (b) (4)  
[REDACTED], the Division has concluded that the CMC and clinical pharmacology data are sufficient to support approval and that the clinical study data are not needed to support the general rheumatoid arthritis indication or the other indications already approved for immediate-release prednisone.

## 12. Labeling

### a. Proprietary Name

The proposed proprietary name Rayos was reviewed by DMEPA and found to be acceptable. The name was also found to be acceptable to OPDP from a promotional perspective.

### b. Physician Labeling

Horizon Pharma submitted a label in the Physician Labeling Rule format. (b) (4)

For reasons discussed above, the label was substantially modified to make it generally consistent with immediate-release prednisone with inclusion of the same indications currently approved for immediate-release prednisone. The label includes clinical pharmacology data related to food effect and the delayed exposure characteristics of Rayos, recommending that the delayed exposure characteristics be taken into consideration so that Rayos is not used in conditions where the delayed release characteristics would be undesirable. For the same reason, there is no specific bedtime dosing recommendation for Rayos. The clinical studies section of the label describes the primary endpoint (ACR 20) and some other secondary endpoints (ACR components, ACR 50, ACR 70, ACR 20 responses over 12 weeks and morning stiffness) from study 007 with balancing disclaimer language stating that a benefit for Rayos compared to immediate-release prednisone has not been established. Inclusion of some secondary endpoints and omission of other secondary endpoints from the Rayos product label are consistent with the Agency's prior precedence with other drugs approved for rheumatoid arthritis (see Appendix 1). The label was reviewed by various disciplines of this Division, the Office of Medical Policy Programs (OMPP), the Office of Surveillance and Epidemiology (OSE)/DMEPA, and by OPDP. Various other changes to different sections of the label were done to reflect the data accurately and better communicate the findings to healthcare providers. The Division and Horizon Pharma have agreed on the final label language.

### c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, ONDQA, OPDP, and DMEPA, and were found to be acceptable.

### d. Patient Labeling and Medication Guide

(b) (4) The review team has concluded that a Medication Guide is not necessary, and Horizon Pharma has agreed. Similar to the reference product, there is no patient labeling.

## 13. Action and Risk Benefit Assessment

### a. Regulatory Action

The submitted data, primarily CMC and clinical pharmacology data, are adequate to support approval of Rayos with the same indications that are approved for immediate-release prednisone. The regulatory action for this application will be approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment supports approval of Rayos for typical indications that immediate-release prednisone has. The CMC and clinical pharmacology data links Rayos to immediate-release prednisone, thereby precluding the need for additional efficacy and safety data for Rayos. The submitted data from the clinical program are consistent with the known efficacy of prednisone in the treatment of rheumatoid arthritis.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

None.

**Appendix 2.**

(b) (4)

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BADRUL A CHOWDHURY  
07/25/2012